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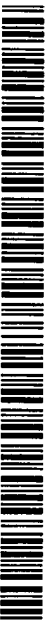
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(54) Title: **G PROTEIN COUPLED RECEPTORS AND USES THEREOF**

(57) Abstract: The present invention provides GPCR polypeptides and polynucleotides, recombinant materials, and transgenic mice, as well as methods for their production. The polypeptides and polynucleotides are useful, for example, in methods of diagnosis and treatment of diseases and disorders. The invention also provides methods for identifying compounds (e.g., agonists or antagonists) using the GPCR polypeptides and polynucleotides of the invention, and for treating conditions associated with GPCR dysfunction with the GPCR polypeptides, polynucleotides, or identified compounds. The invention also provides diagnostic assays for detecting diseases or disorders associated with inappropriate GPCR activity or levels.



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G PROTEIN COUPLED RECEPTORS AND USES THEREOF

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Reference to Table Submitted on Compact Disc

Pursuant to PCT Administrative Instruction § 801(a), Table 35 is submitted herewith in triplicate on compact disc as "50001.007WO3 Table 35.txt," created on September 8, 2003 and having a size of 1,804 kB, hereby incorporated by reference.

10

Background of the Invention

The invention relates to the fields of medicine and drug discovery.

Mammalian G protein coupled receptors (GPCRs) constitute a superfamily of diverse proteins with thousands of members. GPCRs act as receptors for a multitude of different signals. Chemosensory GPCRs (csGPCR) are receptors for sensory signals of external origin that are sensed as odors, pheromones, or tastes. Most other GPCRs respond to endogenous signals, such as peptides, lipids, neurotransmitters, or nucleotides. GPCRs falling in the latter group are involved in numerous physiological processes, including the regulation of neuronal excitability, metabolism, reproduction, development, hormonal homeostasis, and behavior, and are differentially expressed in many cell types in the body.

Of all currently marketed drugs, greater than 30% are modulators of specific GPCRs. Only 10% of GPCRs (excluding csGPCRs) are targeted by these drugs, emphasizing the potential of the remaining 90% of the gene family for the treatment of human disease.

Despite the importance of GPCRs in physiology and disease, the size of the GPCR superfamily is still uncertain. Analyses of genome sequences have generated markedly varied estimates (Venter, J.C. et al., Science 291, 1304-51 (2001); Lander, E.S. et al., Nature 409, 860-921 (2001); Takeda, S. et al., FEBS Lett 520, 97-101 (2002)). In addition, while most GPCRs are known to be selectively expressed in subsets of cells, the expression patterns of most GPCRs are incomplete or unknown. Thus, there is a need for GPCR

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polypeptides, polynucleotides, antibodies, genetic models, and modulating compounds for use in the treatment and diagnosis of a wide variety of disorders and diseases.

Summary of the Invention

5 The present invention provides GPCR polypeptides and polynucleotides, recombinant materials, and transgenic mice, as well as methods for their production. The polypeptides and polynucleotides are useful, for example, in methods of diagnosis and treatment of diseases and disorders. The invention also provides methods for identifying compounds (e.g., agonists or antagonists) using the GPCR polypeptides and polynucleotides
10 of the invention, and for treating conditions associated with GPCR dysfunction with the GPCR polypeptides, polynucleotides, or identified compounds. The invention also provides diagnostic assays for detecting diseases or disorders associated with inappropriate GPCR activity or levels.

 In one aspect, the invention features a variety of substantially pure GPCR
15 polypeptides. Such polypeptides include: (a) polypeptides including a polypeptide sequence having at least 90%, 95%, 97%, 98%, or 99% identity to a polypeptide listed in Table 2; (b) polypeptides that include a polypeptide listed in Table 2; (c) polypeptides having at least 90%, 95%, 97%, 98%, or 99% sequence identity to a polypeptide listed in Table 2; and (d) polypeptides listed in Table 2.

20 Polypeptides of the present invention also include variants of the aforementioned polypeptides, including all allelic forms and splice variants. Such polypeptides vary from the reference polypeptide by insertions, deletions, and substitutions that may be conservative or non-conservative, or any combination thereof. Particularly desirable variants are those in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10,
25 from 10 to 5, from 5 to 3, from 3 to 2, or from 2 to 1 amino acids are inserted, substituted, or deleted, in any combination.

 Polypeptides of the present invention also include polypeptides that include an amino acid sequence having at least 30, 50, or 100 contiguous amino acids from any of the polypeptides listed in Table 2. Polypeptides of the invention are desirably biologically
30 active or are antigenic or immunogenic in an animal, especially in a human.

The polypeptides of the present invention may be in the form of the "mature" polypeptide, or may be a part of a larger polypeptide such as a precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence that contains secretory or leader sequences, pro-sequences, sequences that aid in purification, for instance multiple
5 histidine residues, or an additional sequence for stability during recombinant production.

Polypeptides of the present invention can be prepared in any suitable manner, for instance by isolation from naturally occurring sources, from genetically engineered host cells comprising expression systems, or by chemical synthesis, using for instance automated peptide synthesizers, or a combination of such methods. For example, polypeptides of the
10 invention may be produced by expressing in a cell (e.g., a yeast, bacterial, mammalian, or insect cell) a vector containing a polynucleotide that encodes a GPCR of the invention under condition in which the polypeptide (e.g., one listed in Table 2) is expressed. Means for preparing such polypeptides are well understood in the art.

In another aspect, the invention features substantially pure GPCR polynucleotides.
15 Such polynucleotides include: (a) polynucleotides that include a polynucleotide sequence having at least 90%, 95%, 97%, 98%, or 99% sequence identity to a polynucleotide listed in Table 2; (b) polynucleotides that include a polynucleotide sequence having at least 90%, 95%, 97%, 98%, or 99% sequence identity to the reverse complement of polynucleotide listed in Table 2; (c) polynucleotides that include a polynucleotide listed in Table 2; (d)
20 polynucleotides that are the reverse complement of polynucleotide listed in Table 2; (e) polynucleotides having at least 90%, 95%, 97%, 98%, or 99% sequence identity to a polynucleotide listed in Table 2; (f) polynucleotides having at least 90%, 95%, 97%, 98%, or 99% sequence identity to the reverse complement of polynucleotide listed in Table 2; (g) polynucleotides listed in Table 2; (h) reverse complement of polynucleotides listed in Table
25 2; (i) polynucleotides that include a polynucleotide sequence encoding a polypeptide sequence having at least 90%, 95%, 97%, 98%, or 99% identity to a polypeptide listed in Table 2; (j) polynucleotides including a nucleotide sequence encoding a polypeptide listed in Table 2; and (k) polynucleotides encoding a polypeptide listed in Table 2. Preferred GPCR polynucleotides of the present invention have at least 15, 30, 50 or 100 contiguous
30 nucleotides from any of the polynucleotides listed in Table 2.

In one embodiment, the polynucleotide is operably linked to a promoter for expression of the polypeptide encoded by the polynucleotide. In certain embodiments, the promoter is a constitutive promoter, is inducible by one or more external agents, or is cell-type specific.

5 In another aspect, the invention features a vector that includes a GPCR polynucleotide of the invention, the vector being capable of directing expression of the polypeptide encoded by the polynucleotide in a vector-containing cell.

In another aspect, the invention features a method of preventing or treating a neurological disease or disorder, including introducing into a human an expression vector
10 that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a neurological disease or disorder, including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially
15 identical to a polypeptide listed in any one of Tables 3-14 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a neurological disease or disorder. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33; (b)
20 contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a neurological disease or disorder. The GPCR polypeptide can be in a cell or may be in a cell-free assay system.

25 In yet another aspect, the invention features another method for determining whether a candidate compound is a compound that may be useful for the treatment of a neurological disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14
30 and 33; (b) contacting the transgenic non-human mammal with the candidate compound;

and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a neurological disease or disorder.

5 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a neurological disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33;
10 (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the GPCR polypeptide in the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a neurological disease or disorder.

15 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a neurological disease or disorder. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in any one of Tables 3-14 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid
20 molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a neurological disease or disorder.

In another aspect, the invention features yet another method for determining whether
25 a candidate compound may be useful for the treatment of a neurological disease or disorder. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction between the candidate compound and the polypeptide. Interaction between the compound and the polypeptide indicates that
30 the candidate compound may be useful for the treatment of a neurological disease or

disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a neurological disease or disorder. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein a change in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a neurological disease or disorder. Preferably, the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a neurological disease or disorder. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in one of Tables 3-14 and 33, wherein presence of the mutation indicates that the patient has an increased risk for developing a neurological disease or disorder.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a neurological disease or disorder. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in any one of Tables 3-14 and 33, wherein presence of the polymorphism indicates that the patient has an increased risk for developing a neurological disease or disorder.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the expression level or biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a neurological disease or disorder. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicates that the patient has an increased risk for developing a neurological disease or

disorder.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a neurological disease or disorder. The method includes the step of measuring the patient's expression level of a polypeptide
5 listed in any one of Tables 3-14 and 33, wherein an alteration in the expression, relative to normal, indicates that the patient has an increased risk for developing a neurological disease or disorder. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Preferred neurological diseases or disorders that can be treated or diagnosed using
10 the methods of the invention or for which candidate therapeutic compounds may be identified include, without limitation, abetalipoproteinemia, abnormal social behaviors, absence (petit mal) epilepsy, absence seizures, abulia, acalculia, acidophilic adenoma, acoustic neuroma, acquired aphasia, acquired aphasia with epilepsy (Landau-Kleffner syndrome) specific reading disorder, acquired epileptic aphasia, acromegalic neuropathy,
15 acromegaly, action myoclonus-renal insufficiency syndrome, acute autonomic neuropathy, acute cerebellar ataxia in children, acute depression, acute disseminated encephalomyelitis, acute idiopathic sensory neuronopathy, acute intermittent porphyria, acute mania, acute mixed episode, acute pandysautonomia, acute polymorphic disorder with symptoms of schizophrenia, acute polymorphic psychotic disorder without symptoms of schizophrenia,
20 acute purulent meningitis, addiction, Addison syndrome, adenovirus serotypes, adjustment disorders, adrenal hyperfunction, adrenal hypofunction, adrenoleuk knock out dystrophy, adrenomyeloneuropathy, advanced sleep-phase syndrome, affective disorder syndromes, agenesis of the corpus callosum, agnosia, agoraphobia, agraphia, agyria, agyria-pachygyria, ahylognosia, Aicardi syndrome, AIDS, akathisia, akinesia, akinetic mutism, akinetopsia,
25 alcohol abuse, alcohol dependence syndrome, alcohol neuropathy, alcohol related disorders, alcoholic amblyopia, alcoholic black knock out, alcoholic cerebellar degeneration, alcoholic dementia, alcoholic hallucinosis, alcoholic polyneuropathy, alcohol-induced anxiety disorders, alcohol-induced dementia, alcohol-induced mood disorders, alcohol-induced psychosis, alcoholism, Alexander's syndrome, alexia, alexia with agraphia, alexia
30 without agraphia, alien hand syndrome, Alper's disease, altered sexuality syndromes,

- alternating hemiplegia, Alzheimer's disease, Alzheimer-like senile dementia, Alzheimer-like juvenile dementia, amenorrhea, aminoacidurias, amnesia, amnesia for offences, amok-type reactions, amorphognosia, amphetamine addiction, amphetamine or amphetamine-like related disorders, amphetamine withdrawal, amyloid neuropathy, amyotrophic lateral
- 5 sclerosis, anencephaly, aneurysms, angioblastic meningiomas, Angleman's syndrome, anhidrosis, anisocoria, anomia, anomic aphasia, anorexia nervosa, anosmia, anosognosia, anterior cingulate syndrome, anterograde amnesia, antibiotic-induced neuromuscular blockade, antisocial personality disorder, Anton's syndrome, anxiety and obsessive-compulsive disorder syndromes, anxiety disorders, apathy syndromes, aphasia, aphemia,
- 10 aplasia, apnea, apraxia, arachnoid cyst, archicerebellar syndrome, Arnold-Chiari malformation, arousal disorders, arrhinencephaly, arsenic poisoning, arteriosclerotic Parkinsonism, arteriovenous aneurysm, arteriovenous malformations, aseptic meningeal reaction, Asperger's syndrome, astereognosis, asthenia, astrocytomas, asymbolia, asynergia, ataque de nervios, ataxia, ataxia telangiectasia, ataxic cerebral palsy, ataxic dysarthria,
- 15 athetosis, atonia, atonic seizures, attention deficit disorder, attention-deficit and disruptive behavior disorders, attention-deficit hyperkinetic disorders, atypical Alzheimer's disease, atypical autism, autism, autism spectrum disorder, avoidant personality disorder, axial dementias, bacterial endocarditis, bacterial infections, Balint's syndrome, ballism, balo disease, basophilic adenoma, Bassen-Knock outnmzweig syndrome, Batten disease, battered
- 20 woman syndrome, Behçet syndrome, Bell' palsy, benign essential tremor, benign focal epilepsies of childhood, benign intracranial hypertension, benxodiazepine dependence, bilateral cortical dysfunction, Binswanger's disease, bipolar disorder, bipolar type 1 disorder, bipolar type 2 disorder, blepharospasm, body dysmorphic disorder, Bogaert-Bertrand disease, Bogarad syndrome, borderline personality disorder, botulism, Bouffée
- 25 Délirante-type reactions, brachial neuropathy, bradycardia, bradykinesia, brain abscess, brain edema, brain fag, brain stem glioma, brainstem encephalitis, brief psychotic disorder, broca's aphasia, brucellosis, bulimia, bulimia nervosa, butterfly glioma, cachexia, caffeine related disorders, california encephalitis, callosal agenesis, Canavan's syndrome, cancer pain, cannabis dependence, cannabis flashbacks, cannabis psychosis, cannabis related
- 30 disorders, carcinoma-associated retinopathy, cardiac arrest, cavernous malformations,

cellular (cytotoxic) edema, central facial paresis, central herniation syndrome, central neurogenic hyperventilation, central pontine myelinolysis, central post-stroke syndrome (thalamic pain syndrome), cerebellar hemorrhage, cerebellar tonsillar herniation syndrome, cerebral amyloid (conophilic) angiopathy, cerebral hemorrhage, cerebral malaria, cerebral palsy, cerebral subdural empyema, cerebrotendinous xanthomatosis, cerebrovascular disorders, cervical tumors, cestodes, Charcot-Carrie-tooth disease, Chediak-Cigashi disease, Cheiro-oral syndrome, chiari malformation with hydrocephalus, childhood disintegrative disorder, childhood feeding problems, childhood sleep problems, cholesteatomas, chordomas, chorea, chorea gravidarum, choreoathetosis, chromophobe adenoma,

5 chromosomal disorders, chronic biplar major depression, chronic bipolar disorder, chronic demyelinating polyneuritis, chronic depression, chronic fatigue syndrome, chronic gm2 gangliosidosis, chronic idiopathic sensory neuropathy, chronic inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, chronic pain, chronic paroxysmal hemicrania, chronic sclerosing panencephalitis, chronic traumatic

10 encephalopathy, chronobiological disorders, circadian rhythm disorder, circadian rhythm disorders, Claude's syndrome, clonic seizures, cluster headache, cocaine addiction, cocaine withdrawal, cocaine-related disorders, Cockayne's syndrome, colloid cysts of the third ventricle, colorado tick fever, coma, communicating hydrocephalus, communication disorders, complex partial seizures, compression neuropathy, compulsive buying disorder,

15 conceptual apraxia, conduct disorders, conduction aphasia, conduction apraxia, congenital analgesia, congenital cytomegalovirus disease, congenital hydrocephalus, congenital hypothyroidism, congenital muscular dystrophy, congenital myasthenia, congenital myotonic dystrophy, congenital rubella syndrome, conophilic angiopathy, constipation, coprophilia, cornelia de lange syndrome, cortical dementias, cortical heteropias,

20 corticobasal degeneration, corticobasal ganglionic degeneration, coxsackievirus, cranial meningoceles, craniopharyngioma, craniorachischisis, craniosynostosis, cranium bifidum, cretinism, Creutzfeldt-Jaknock outb disease, Cri-du-Chat syndrome, cruciate hemiplegia, cryptococcal granulomas, cryptococcosis, culturally related syndromes, culturally stereotyped reactions to extreme environmental conditions (arctic hysteria), Cushing

25 syndrome, cyclothymia, cysticercosis, cytomegalovirus, Dandy-Walker malformation,

30

deafness, defects in the metabolism of amino acids, dehydration, Dejerine-Roussy syndrome, Dejerine-Sottas disease, delayed and advanced sleep phase syndromes, delayed ejaculation, delayed puberty, delayed-sleep-phase syndrome, delerium due to alcohol, delerium due to intoxication, delerium due to withdrawal, delirium, dementia, and amnesic

5 and other cognitive disorders, delusional disorder, delusional disorder: erotomania subtype, delusional disorder: grandiose subtype, delusional disorder: jealousy subtype, delusional misidentification syndromes, dementia due to HIV disease, dementia pugilistica, dementias, dementias associated with extrapyramidal syndrome, dentatorubral-pallidoluysian atrophy, dependent personality disorder, depersonalization disorder, depression, depressive

10 personality disorder, dermoids, developmental speech and language disorder, devic syndrome, devivo disease, diabetes, diabetes insipidus, diabetic neuropathy, dialysis demential, dialysis dysequilibrium syndrome, diencephalic dementias, diencephalic dysfunction, diencephalic syndrome of infancy, diencephalic vascular dementia, diffuse sclerosis, digestive disorders, diphtheria, diplopia, disarthria, disassociation apraxia,

15 disorders of carbohydrate metabolism, disorders of excessive somnolence, disorders of metal metabolism, disorders of purine metabolism, disorders of sexual arousal, disorders of sexual aversion, disorders of sexual desire, disorders of the sleep-wake schedule, dissociative disorders, dorsolateral tegmental pontine syndrome, Down syndrome, Down syndrome with dementia, drug dependance, drug overdose, drug-induced myasthenia,

20 Duchenne muscular dystrophy, dwarfism, dysarthria, dysdiadochokinesia, dysembryoplastic neuroepithelial tumor, dysexecutive syndrome, dysgraphia, dyskinesia, dyskinetic cerebral palsy, dyslexia, dysmetria, dysomnia, dysosmia, dyspareunia, dysphagia, dysphasia, dysphonia, dysplasia, dyspnea, dysprosody, dyssomnia, dyssynergia, dyesthesia, dysthymia, dystonia, dystrophinopathies, early adolescent gender identity disorder, early infantile

25 epileptic encephalopathy (Ohtahara syndrome, early myoclonic epileptic encephalopathy, Eaton-Lambert syndrome, echinococcus (hydatid cysts), echolalia, echovirus, eclampsia, Edward's syndrome, elimination disorders, embolismintracerebral hemorrhage, Emery-Dreifuss muscular dystrophy, encephalitis lethargica, encephaloceles, encephalotrigeminal angiomatosis, enophthalmos, enterovirus, enuresis, eosinophilic meningitis, ependymoma,

30 epidural spinal cord compression, epilepsy, episodic ataxia, epstein-barr, equine

- encephalomyelitis, erectile dysfunction, essential thrombocythemia, essential tremor, esthesioneuroblastoma, excessive daytime somnolence, excessive secretion of antidiuretic hormone, excessive sleepiness, exhibitionism, expressive language disorder, extramedullary tumors, extrasylvian aphasias, extratemporal neocortical epilepsy, fabry's disease,
- 5 facioscapulohumeral muscular dystrophy, factitious disorder, factitious disorders, false memories, familial dysautonomia, familial periodic paralysis, familial spastic paraparesis, familial spastic paraplegias, fear disorders, feeding and eating disorders of infancy or early childhood, female sexual arousal disorder, fetal alcohol syndrome, fetishism, flaccid dysarthria, floppy infant syndrome, focal inflammatory demyelinating lesions with mass
- 10 effect, focal neonatal hypotonia, folie à deux, foramen magnum tumors, Foville's syndrome, fragile-x syndrome, Freidrich 's ataxia, Frolich syndrome, frontal alexia, frontal convexity syndrome, frontotemporal dementia, frontotemporal dementias, frotteurism, fungal infection, galactocerebroside lipidosis, galactorrhea, ganglioneuroma, Gaucher disease, gaze palsy, gender identity disorder, generalized anxiety disorder, genital shrinking syndrome
- 15 (Knock out, Suo-Yang), germ cell tumors, Gerstmann's syndrome, Gerstmann-Straüssler syndrome, Gerstmann-Straussler-Schenker disease, Gertmann's syndrome, gestational substance abuse syndromes, giant axonal neuropathy, gigantism, Gilles de la Tourette syndrome, glioblastoma multiforme, gliomas, gliomatosis cerebri, global aphasia, glossopharyngeal neuralgia, glycogen storage diseases, gm1-gangliosidosis, gm2-
- 20 gangliosidoses, granular cell tumor, granulocytic brain edema, granulomas, granulomatous angiitis of the brain, Grave's disease, growild typeh hormone deficit , growild typeh-hormone secreting adenomas, guam-Parkinson complex dementia, Guillain-Barré syndrome, Hallervorden-Spatz disease, hallucinogen persisting perception disorder, hallucinogen related disorders, hartnup disease, headache, helminthic infections
- 25 (trichinellosis), hemangioblastomas, hemangiopericytomas, hemiachromatopsia, hemianesthesia, hemianopsia, hemiballism, hemiballismus, hemihypacusis, hemihypesthesia, hemiparesis, hemispatial neglect, hemophilus influenza meningitis, hemorrhagic cerebrovascular disease, hepatic coma, hepatic encephalopathy, hepatolenticular degeneration (Wilson disease), hereditary amyloid neuropathy, hereditary
- 30 ataxias, hereditary cerebellar ataxia, hereditary neuropathies, hereditary nonprogressive

- chorea, hereditary predisposition to pressure palsies, hereditary sensory autonomic neuropathy, hereditary sensory neuropathy, hereditary spastic paraplegia, hereditary tyrosinemia, hermichorea, hermifacial spasm, herniation syndromes, herpes encephalitis, herpes infections, herpes zoster, herpes simplex, heterotopia, hexacarbon neuropathy,
- 5 histrionic personality disorder, HIV, Holmes-Adie syndrome, homonymous quadrantanopsia, Horner's syndrome, human β -mannosidosis, Hunter's syndrome, Huntington's chorea, Huntington's disease, Hurler's syndrome, Hwa-Byung, hydraencephaly, hydrocephalus, hyper thyroidism, hyperacusis, hyperalgesia, hyperammonemia, hypereosinophilic syndrome, hyperglycemia, hyperkalemic periodic paralysis, hyperkinesia, hyperkinesis,
- 10 hyperkinetic dysarthria, hyperosmia, hyperosmolar hyperglycemic nonketonic diabetic coma, hyperparathyroidism, hyperphagia, hyperpituitarism, hyperprolactinemia, hypersexuality, hypersomnia, hypersomnia secondary to drug intake, hypersomnia-sleep-apnea syndrome, hypersomnolence, hypertension, hypertensive encephalopathy, hyperthermia, hyperthyroidism (Graves disease), hypertonia, hypnagogic (predormital)
- 15 hallucinations, hypnogenic paroxysmal dystonia, hypoadrenalism, hypoalgesia, hypochondriasis, hypoglycemia, hypoinsulinism, hypokalemic periodic paralysis, hypokinesia, hypokinetic dysarthria, hypomania, hypoparathyroidism, hypophagia, hypopituitarism, hypoplasia, hyposmia, hyposthenuria, hypotension, hypothermia, hypothyroid neuropathy, hypothyroidism, hypotonia, Hyrler syndrome, hysteria, ideational
- 20 apraxia, ideomotor apraxia, idiopathic hypersomnia, idiopathic intracranial hypertension, idiopathic orthostatic hypotension, immune mediated neuropathies, impersistence, impotence, impulse control disorders, impulse dyscontrol and aggression syndromes, impulse-control disorders, incontinence, incontinentia pigmenti, infantile encephalopathy with cherry-red spots, infantile neuraxonal dystrophy, infantile spasms, infantilism,
- 25 infarction, infertility, influenza, inhalant related disorders, insomnias, insufficient sleep syndrome, intention tremor, intermittent explosive disorder, internuclear ophthalmoplegia, interstitial (hydrocephalic) edema, intoxication, intracranial epidural abscess, intracranial hemorrhage, intracranial hypotension, intracranial tumors, intracranial venous-sinus thrombosis, intradural hematoma, intramedullary tumors, intravascular lymphoma,
- 30 ischemia, ischemic brain edema, ischemic cerebrovascular disease, ischemic neuropathies,

isolated inflammatory demyelinating CNS syndromes, Jackson-Collet syndrome, Jaknock
 outb-Creutzfeld disease, Japanese encephalitis, jet lag syndrome, Joseph disease, Joubert's
 syndrome, juvenile neuroaxonal dystrophy, Kayak-Svimmel, Kearns-Sayre syndrome,
 kinky hair disease (Menkes syndrome), Kleine-Levin syndrome, kleptomania, Klinefelter's
 5 syndrome, Kluver-Bucy syndrome, Knock outerber-Salus-Elschnig syndrome, Knock
 outsaknock outff's syndrome, krabbe disease, krabbe leuknock outdystrophy, Kugelberg-
 Welanders syndrome, kuru, Lafora's disease, language deficits, language related disorders,
 latah-type reactions, lateral mass herniation syndrome, lateropulsation, lathyrism, Laurence-
 Moon Biedl syndrome, Laurence-Moon syndrome, lead poisoning, learning disorders, leber
 10 hereditary optic atrophy, left ear extinction, legionella pneumophilia infection, Leigh's
 disease, Lennoc-Gastaut syndrome, Lennox-Gastaut's syndrome, leprosy, leptospirosis,
 Lesch-Nyhan syndrome, leukemia, leuknock outdystrophies, Lévy-Roussy syndrome, lewy
 body dementia, lewy body disease, limb girdle muscular dystrophies, limbic encephalitis,
 limbic encephalopathy, lissencephaly, localized hypertrophic neuropathy, locked-in
 15 syndrome, logoclonia, low pressure headache, Lowe syndrome, lumbar tumors, lupus
 anticoagulants, lyme disease, lyme neuropathy, lymphocytic choriomeningitis, lymphomas,
 lysosomal and other storage diseases, macroglobinemia, major depression with melancholia,
 major depression with psychotic features, major depression without melancholia, major
 depressive (unipolar) disorder, male orgasmic disorder, malformations of septum
 20 pellucidum, malignant peripheral nerve sheath tumors, malingers, mania, mania with
 psychotic features, mania without psychotic features, maple syrup urine disease,
 Marchiafava-Bignami syndrome, Marcus Gunn syndrome, Marie-Foix syndrome,
 Marinesco-Sjögren syndrome, Maroteaux-Lamy syndrome, masochism, masturbatory pain,
 measles, medial frontal syndrome, medial medullary syndrome, medial tegmental
 25 syndrome, medication-induced movement disorders, medullary dysfunction,
 medulloblastomas, medulloepithelioma, megalencephaly, melanocytic neoplasms, memory
 disorders, memory disturbances, meniere syndrome, meningeal carcinomatosis, meningeal
 sarcoma, meningial gliomatosis, meningiomas, meningism, meningitis, meningococcal
 meningitis, mental neuropathy (the numb chin syndrome), mental retardation, mercury
 30 poisoning, metabolic neuropathies, metachromatic leuknock outdystrophy, metastatic

neuropathy, metastatic tumors, metazoal infections, microcephaly, microencephaly,
 micropolygyria, midbrain dysfunction, midline syndrome, migraine, mild depression,
 Millard-Gubler syndrome, Miller-Dieker syndrome, minimal brain dysfunction syndrome,
 miosis, mitochondrial encephalopathy with lactic acidosis and stroke (melas), mixed
 5 disorders of scholastic skills, mixed dysarthrias, mixed transcortical aphasia, Möbius
 syndrome, Mollaret meningitis, monoclonal gammopathy, mononeuritis multiplex,
 monosymptomatic hypochondriacal psychosis, mood disorders, Moritz Benedikt syndrome,
 Morquio syndrome, Morton's neuroma, motor neuron disease, motor neurone disease with
 dementia, motor neuropathy with multifocal conduction block, motor skills disorder ,
 10 mucopolipidoses, mucopolysaccharide disorders, mucopolysaccharidoses, multifocal
 eosinophilic granuloma, multiple endocrine adenomatosis, multiple myeloma, multiple
 sclerosis, multiple system atrophy, multiple systems atrophy, multisystemic degeneration
 with dementia, mumps, Munchausen syndrome, Munchausen syndrome by proxy, muscular
 hypertonia, mutism, myasthenia gravis, mycoplasma pneumoniae infection, myoclonic
 15 seizures, myoclonic-astatic epilepsy (doose syndrome), myoclonus, myotonia congenita,
 myotonic dystrophy, myotonic muscular dystrophy, narcolepsy, narcissistic personality
 disorder, narcolepsy, narcolepsy-cataplexy syndrome, necrophilia, nectrotizing
 encephalomyelopathy, Nelson's syndrome, neocerebellar syndrome, neonatal myasthenia,
 neonatal seizures, nervios, nerves, neurasthenia, neuroacanthocytosis, neuroaxonal
 20 dystrophy, neurocutaneous disorders, neurofibroma, neurofibromatosis, neurogenic
 orthostatic hypotension, neuroleptic malignant syndrome, neurologic complications of renal
 transplantation, neuromyelitis optica, neuromyotonia (Isaacs syndrome), neuronal ceroid
 lipofuscinoses, neuro-ophthalmic disorders, neuropathic pain , neuropathies associated
 with infections, neuropathy associated with cryoglobulins, neuropathy associated with
 25 hepatic diseases, neuropathy induced by cold, neuropathy produced by chemicals,
 neuropathy produced by metals, neurosyphilis, new variant Creutzfeldt-Jaknock outb
 disease, nicotine dependence, nicotine related disorders, nicotine withdrawal, niemann-pick
 disease, nocturnal dissociative disorders, nocturnal enuresis, nocturnal myoclonus,
 nocturnal sleep-related eating disorders, neocerebellar syndrome, non-alzheimer frontal-lobe
 30 degeneration, nonamyloid polyneuropathies associated with plasma cell dyscrasia, non-

lethal suicidal behavior, nonlocalizing aphasic syndromes, normal pressure hydrocephalus,
 Nothnagel's syndrome, nystagmus, obesity, obsessive-compulsive (anankastic) personality
 disorder, obsessive-compulsive disorder, obstetric factitious disorder, obstructive
 hydrocephalus, obstructive sleep apnea, obstructive sleep apnoea syndrome, obstructive sleep
 5 hypopnoea syndrome, occipital dementia, occlusive cerebrovascular disease,
 oculocerebrorenal syndrome of Lowe, oculomotor nerve palsy, oculopharyngeal muscular
 dystrophy, oligodendrogliomas, olivopontocerebellar atrophy, Ondine's curse, one and a half
 syndrome, onychophagia, opiate dependence, opiate overdose, opiate withdrawal, opioid
 related disorders, oppositional defiant disorder, opsoclonus, orbitofrontal syndrome,
 10 orgasmic anhedonia, orgasmic disorders, osteosclerotic myeloma, other disorders of
 infancy, childhood, or adolescence, other medication-induced movement disorders,
 pachygyria, paedophilia, pain, pain syndromes, painful legs-moving toes syndrome,
 paleocerebellar syndrome, palilalia, panhypopituitarism, panic disorder, panic disorders,
 papillomas of the choroid plexus, paraganglioma, paragonimiasis, paralysis, paralysis
 15 agitans (shaking palsy), paramyotonia congenita, paraneoplastic cerebellar degeneration,
 paraneoplastic cerebellar syndrome, paraneoplastic neuropathy, paraneoplastic syndromes,
 paranoia, paranoid personality disorder, paranoid psychosis, paraphasia, paraphilias,
 paraphrenia, parasitic infections, parasomnia, parasomnia overlap disorder, parenchymatous
 cerebellar degeneration, paresis, paresthesia, Parinaud's syndrome, Parkinson's disease,
 20 Parkinson-dementia complex of Guam, Parkinsonism, Parkinsonism-plus syndromes,
 Parkinson's disease, paroxysmal ataxia, paroxysmal dyskinesia, partial (focal) seizures,
 partialism, passive-aggressive (negativistic) personality disorder, Patau's syndrome,
 pathological gambling, peduncular hallucinosis, Pelizaeus-Merzbacher disease,
 perineurioma, peripheral neuropathy, perisylvian syndromes, periventricular leukoencephalopathy,
 25 outstria, periventricular white matter disorder, periventricular-intraventricular
 hemorrhage, pernicious anemia, peroneal muscular atrophy, peroxisomal diseases,
 perseveration, persistence of cavum septi pellucidi, persistent vegetative state, personality
 disorders, pervasive developmental disorders, phencyclidine (or phencyclidine-like) related
 disorders, phencyclidine delirium, phencyclidine psychosis, phencyclidine-induced
 30 psychotic disorder, phenylketonuria, phobic anxiety disorder, phonic tics, photoreceptor

degeneration, pibloktoq, Pick's disease, pineal cell tumors, pineoblastoma, pineocytoma,
 pituitary adenoma, pituitary apoplexy, pituitary carcinoma, pituitary dwarfism, placebo
 effect, Plummer's disease, pneumococcal meningitis, poikilothermia, polio, polycythemia
 vera, polydipsia, polyglucosan storage diseases, polymicrogyria, polymyositis,
 5 polyneuropathy with dietary deficiency states, polysubstance related disorder, polyuria,
 pontine dysfunction, pontosubicular neuronal necrosis, porencephaly, porphyric neuropathy,
 portal-systemic encephalopathy, postcoital headaches, postconcussion syndrome,
 postencephalic Parkinson syndrome, posthemorrhagic hydrocephalus, postinflammatory
 hydrocephalus, postpartum depression, postpartum psychoses, postpolio syndrome,
 10 postpsychotic depression, post-stroke hypersomnia, post-traumatic amnesia, post-traumatic
 epilepsy, post-traumatic hypersomnia, post-traumatic movement disorders, post-traumatic
 stress disorder, post-traumatic syndromes, Prader-Willi syndrome, precocious puberty,
 prefrontal dorsolateral syndrome, prefrontal lobe syndrome, premenstrual stress disorder,
 premenstrual syndrome, primary amebic meningoencephalitis, primary CNS lymphoma,
 15 primary idiopathic thrombosis, primary lateral sclerosis, primitive neuroectodermal tumors,
 prion disease, problems related to abuse or neglect, progressive bulbar palsy, progressive
 frontal lobe dementias, progressive multifocal lueknock outencephalopathy, progressive
 muscular atrophy, progressive muscular dystrophies, progressive myoclonic epilepsies,
 progressive myoclonus epilepsies, progressive non-fluent aphasia, progressive partial
 20 epilepsies, progressive rubella encephalitis, progressive sclerosing poliodystrophy (Alpers
 disease), progressive subcortical gliosis, progressive supranuclear palsy, progressive
 supranuclear paralysis, progrssive external ophthalmoplegia, prolactinemia , prolactin-
 secreting adenomas, prosopagnosia, protozoan infection, pseudobulbar palsy, pseudocyesis,
 pseudodementia, psychic blindness, psychogenic excoriation, psychogenic fugue,
 25 psychogenic pain syndromes, psychological mutism, psychosis after brain injury, psychotic
 syndromes, ptosis, public masturbation, puerperal panic, pulmonary edema, pure word
 deafness, pyromania, quadrantanopsia, rabies, radiation neuropathy, Ramsay Hunt
 syndrome, rape traume syndrome, rapid cycling disorder, rapid ejaculation, Raymond-
 Cestan-Chenais syndrome, receptive language disorder, recovered memories, recurrent
 30 bipolar episodes, recurrent brief dpression, recurrent hypersomnia, recurrent major

depression, refsum disease, reiterative speech disturbances, relational problems, rem sleep behavior disorder, rem sleep behavioral disorder, repetitive self-mutilation, repressed memories, respiratory dysrhythmia, restless legs syndrome, Rett's syndrome, Reye syndrome, rhythmic movement disorders, rocky mountain spotted fever, rostral basal pontine syndrome, rubella, Rubinstein-Taybi syndrome, sadistic personality disorder, salla disease, Sandhoff disease, Sanfilippo syndrome, sarcoid neuropathy, sarcoidosis, scapuloperoneal syndromes, schistosomiasis (bilharziasis), schizencephaly, schizoaffective disorder, schizoid personality disorder, schizophrenia, schizophrenia and other psychotic disorders, schizophrenia-like psychosis, schizophreniform disorder, schizotypal personality disorder, school-refusal anxiety disorder, schwannoma, scrub typhus, seasonal depression, secondary spinal muscular atrophy, secondary thrombosis, sedative hypnotic or anxiolytic-related disorders, seizure disorders, selective mutism, self-defeating (masochistic) personality disorder, semen-loss syndrome (shen-k'uei, dhat, jiryan, sukra prameha), senile chorea, senile dementia, sensory perineuritis, separation anxiety disorder, septal syndrome, septo-optic dysplasia, severe hypoxia, severe myoclonic epilepsy, sexual and gender identity disorders, sexual disorders, sexual dysfunctions, sexual pain disorders, sexual sadism, Shapiro syndrome, shift work sleep disorder, Shy-Drager syndrome, sialidosis, sialidosis type 1, sibling rivalry disorder, sickle cell anemia, Simmonds disease, simple partial seizures, simultanagnosia, sleep disorders, sleep paralysis, sleep terrors, sleep-related enuresis, sleep-related gastroesophageal reflux syndrome, sleep-related headaches, sleep-wake disorders, sleepwalking, Smith-Magenis syndrome, social anxiety disorder, social phobia, social relationship syndromes, somatoform disorders, somnambulism, Sotos syndrome, spasmodic dysphonia, spasmodic torticollis (wry neck), spastic cerebral palsy, spastic dysarthria, specific developmental disorder of motor function, specific developmental disorders of scholastic skills, specific developmental expressive language disorder, specific developmental receptive language disorder, specific disorders of arithmetical skills, specific phobia, specific speech articulation disorder, specific spelling disorder, speech impairment, spina bifida, spinal epidural abcess, spinal muscular atrophies, spinocerebellar ataxias, spirochete infections, spongiform encephalopathies, spongy degeneration of the nervous system, St. Louis encephalitis, stammer, staphylococcal

- meningitis, startle syndromes, status marmoratus, steele-richardson-olszewski syndrome, stereotypic movement disorder, stereotypies, stiff-man syndrome, stiff-person syndrome, stimulant psychosis, Strachan syndrome (nutritional neuropathy), streptococcal meningitis, striatonigral degeneration, stroke, strongyloidiasis, sturge-weber disease (Krabbe-Weber-Dimitri disease), stutter, subacute combined degeneration of the spinal cord, subacute motor neuronopathy, subacute necrotic myelopathy, subacute sclerosing panencephalitis, subacute sensory neuronopathy, subarachnoid hemorrhage, subcortical aphasia, subfalcine herniation syndrome, substance abuse, substance related disorders, sudanophilic leukoencephalopathy, sudden infant death syndrome, suicide, sulfatide lipidosis, susto, espanto, meido, sydenham chorea, symmetric neuropathy associated with carcinoma, sympathotonic orthostatic hypotension, syncope, syndromes related to a cultural emphasis on learnt dissociation, syndromes related to a cultural emphasis on presenting a physical appearance pleasing to others (taijin-kyofu reactions), syndromes related to acculturative stress, syringobulbia, syringomyelia, systemic lupus erythematosus, tachycardia, tachypnea,
- 15 Tangier disease, tardive dyskinesia, Tay-sachs disease, telangiectasia, telencephalic leukoencephalopathy, telephone scatologia, temporal lobe epilepsy, temporoparietal dementia, tension-type headache, teratomas, tetanus, tetany, thalamic syndrome, thallium poisoning, thoracic tumors, thrombotic thrombocytopenic purpura, thyroid disorders, tic disorders, tick paralysis, tick-borne encephalitis, tinnitus, toxic neuropathy, tonic seizures, tonic-clonic seizures, torticollis, Tourette syndrome, toxic neuropathies,
- 20 toxoplasmosis, transcortical motor aphasia, transcortical sensory aphasia, transient epileptic amnesia, transient global amnesia, transitional sclerosis, transvestic fetishism, traumatic brain injury, traumatic neuroma, traumatic mutism, tremors, trichinosis, trichotillomania, trigeminal neuralgia, trochlear nerve palsy, tropical ataxic neuropathy, tropical spastic paraparesis, trypanosomiasis, tuberculomas, tuberculous meningitis, tuberous sclerosis,
- 25 tumors, Turner's syndrome, typhus fever, ulegyria, unciniate fits, Unverricht-Lundborg's disease, upper airway resistance syndrome, upward transtentorial herniation syndrome, uremic encephalopathy, uremic neuropathy, urophilia, vaccinia, varicella-zoster, vascular dementia, vascular malformations, vasculitic neuropathies, vasogenic edema,
- 30 velocardiofacial syndrome, venous malformations, ventilatory arrest, vertigo, vincristine

toxicity, viral infections, visuospatial impairment, Vogt-Knock outyanagi-Harada syndrome, Von Hippel-Lindau disease, Von Racklinghausen disease, voyeurism, Waldenström's macroglobulinemia, Walker-Warburg syndrome, Wallenburg's syndrome, Walleyed syndrome, Weber's syndrome, Wernicke's encephalopathy, Werdnig-Hoffmann disease, Wernicke's encephalopathy, Wernicke-Knock outsaknock outff syndrome, Wernicke's aphasia, West's syndrome, whipple disease, Williams syndrome, Wilson disease, windigo, witiknock out, witigo, withdrawal with grand mal seizures, withdrawal with perceptual disturbances, withdrawal without complications, Wolman disease, xeroderma pigmentosum, xyy syndrome, Zellweger syndrome.

10 Neurological diseases and disorders that are treated or diagnosed by methods of the invention or for which candidate therapeutic compounds are identified preferably involve at least one of the following neurological tissues: hypothalamus, amygdala, pituitary, nervous system, brainstem, cerebellum, cortex, frontal cortex, hippocampus, striatum, and thalamus or other regions of the central or peripheral nervous system.

15 In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33.

 In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially
20 identical to a polypeptide listed in any one of Tables 3-14 and 33.

 In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33.

 In another aspect, the invention features a cell from a non-human mammal having a
25 mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33.

 In another aspect, the invention features a method of preventing or treating a disease of the adrenal gland including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide
30 listed in Tables 15 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a disease of the adrenal gland including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33.

- 5 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the adrenal gland. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring
10 biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland. The GPCR polypeptide can be in a cell or in a cell-free assay system.

- In yet another aspect, the invention features a method for determining whether a
15 candidate compound is a compound that may be useful for the treatment of a disease or disorder of the adrenal gland. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33; (b) contacting the transgenic non-human mammal with the candidate
20 compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland.

- In yet another aspect, the invention features a method for determining whether a
25 candidate compound is a compound that may be useful for the treatment of a disease or disorder of the adrenal gland. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c)
30 measuring biological activity of the GPCR polypeptide in the transgenic non-human

mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 15 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the adrenal gland. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient

has an increased risk for developing a disease or disorder of the adrenal gland. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 15 and 33, wherein presence of the mutation indicates that the patient has an increased risk for developing a disease or disorder of the adrenal gland.

5 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the adrenal gland. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 15 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of
10 the adrenal gland.

 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

 In another aspect, the invention features another method for determining whether a
15 patient has an increased risk for developing a disease or disorder of the adrenal gland. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 15 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicates that the patient has an increased risk for developing a disease or disorder of the adrenal gland.

20 In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the adrenal gland. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 15 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of
25 the adrenal gland. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

 Diseases of the adrenal gland that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include 11-hydroxylase deficiency, 17-hydroxylase deficiency, 3 β -dehydrogenase deficiency, acquired
30 immune deficiency syndrome, ACTH-dependent adrenal hyperfunction (Cushing disease),

ACTH-independent adrenal hyperfunction, acute adrenal insufficiency, adrenal abscess, adrenal adenoma, adrenal calcification, adrenal cysts, adrenal cytomegaly, adrenal dysfunction in glycerol kinase deficiency, adrenal hematoma, adrenal hemorrhage, adrenal histoplasmosis, adrenal hyperfunction, adrenal hyperplasia, adrenal medullary hyperplasia, adrenal myelolipoma, adrenal tuberculosis, adrenocortical adenoma, adrenocortical adenoma with primary hyperaldosteronism (Conn's syndrome), adrenocortical carcinoma, adrenocortical carcinoma with Cushing's syndrome, adrenocortical hyperfunction, adrenocortical insufficiency, adrenocortical neoplasms, adrenoleukodystrophy, amyloidosis, anencephaly, autoimmune Addison's disease, Beckwith-Wiedemann syndrome, bilateral adrenal hyperplasia, chronic insufficiency of adrenocortical hormone synthesis, complete 21-hydroxylase deficiency, congenital adrenal hyperplasia, congenital adrenal hypoplasia, cortical hyperplasia, desmolase deficiency, ectopic ACTH syndrome, excess aldosterone secretion, excess cortisol secretion (Cushing's syndrome), excess secretion of adrenocortical hormones, excess sex hormone secretion, familial glucocorticoid deficiency, functional "black" adenomas, ganglioneuroblastoma, ganglioneuroma, glucocorticoid remediable hyperaldosteronism, herpetic adrenalitis, hyperaldosteronism, idiopathic Addison's disease, idiopathic hyperaldosteronism with bilateral hyperplasia of zona glomerulosa, iatrogenic hypercortisolism, lysosomal storage diseases, macronodular hyperplasia, macronodular hyperplasia with marked adrenal enlargement, malignant lymphoma, malignant melanoma, metastatic carcinoma, metastatic tumors, micronodular hyperplasia, multiple endocrine neoplasia syndromes, multiple endocrine neoplasia type 1 (Wermer syndrome), multiple endocrine neoplasia type 2a (Sipple syndrome), multiple endocrine neoplasia type 2b, neuroblastoma, Niemann-Pick disease, ovarian thecal metaplasia, paraganglioma, partial 21-hydroxylase deficiency, pheochromocytoma, primary aldosteronism (Conn's syndrome), primary chronic adrenal insufficiency (Addison's disease), primary hyperaldosteronism, primary mesenchymal tumors, primary pigmented nodular adrenocortical disease, salt-wasting congenital adrenal hyperplasia, secondary Addison's disease, secondary hyperaldosteronism, selective hypoaldosteronism, simple virilizing congenital adrenal hyperplasia, Waterhouse-Friderichsen syndrome, and Wolman's disease.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 15.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse),
5 having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 15.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 15.

10 In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 15.

In another aspect, the invention features a method of preventing or treating a disease of the colon including introducing into a human an expression vector that includes a nucleic
15 acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a disease of the colon including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a
20 polypeptide listed in Tables 16 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the colon. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33; (b) contacting the GPCR
25 polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the colon. The GPCR polypeptide can be in a cell or in a cell-free assay system.

30 In yet another aspect, the invention features a method for determining whether a

candidate compound is a compound that may be useful for the treatment of a disease or disorder of the colon. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the colon.

10 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the colon. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33; (b) 15 contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the colon.

20 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the colon. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 16 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with 25 the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the colon.

In another aspect, the invention features yet another method for determining whether 30 a candidate compound may be useful for the treatment of a disease or disorder of the colon.

This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate
5 compound may be useful for the treatment of a disease or disorder of the colon.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the colon. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33; (b) contacting the polypeptide with the
10 candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the colon. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

15 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the colon. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 16 and 33, wherein presence of the mutation indicates that the patient has an increased risk for developing a disease or disorder of the colon.

20 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the colon. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 16 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the colon.

25 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the colon. The method
30 includes measuring biological activity of a GPCR polypeptide from the patient that is

substantially identical to a polypeptide listed in Tables 16 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the colon.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the colon. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 16 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the colon. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the colon that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include acute self-limited infectious colitis, adenocarcinoma, adenoma, adenoma-carcinoma sequence, adenomatous polyposis coli, adenosquamous carcinomas, allergic (eosinophilic) proctitis and colitis, amebiasis, amyloidosis, angiodysplasia, anorectal malformations, blue rubber bleb nevus syndrome, brown bowel syndrome, *Campylobacter fetus* infection, carcinoid tumors, carcinoma of the anal canal, carcinoma of the colon and rectum, chlamydial proctitis, Crohn's disease, clear cell carcinomas, *Clostridium difficile* pseudomembranous enterocolitis, collagenous colitis, colonic adenoma, colonic diverticulosis, colonic inertia, colonic ischemia, congenital atresia, congenital megacolon (Hirschsprung's disease), congenital stenosis, constipation, Cowden's syndrome, cystic fibrosis, cytomegalovirus colitis, diarrhea, dieulafor lesion, diversion colitis, diverticulitis, diverticulosis, drug-induced diseases, dysplasia and malignancy in inflammatory bowel disease, Ehlers-Danlos syndromes, enterobiasis, familial adenomatous polyposis, familial polyposis syndromes, Gardner's syndrome, gastrointestinal stromal neoplasms, hemangiomas and vascular anomalies, hemorrhoids, hereditary hemorrhagic telangiectasia, herpes colitis, hyperplastic polyps, idiopathic inflammatory bowel disease, incontinence, inflammatory bowel syndrome, inflammatory polyps, inherited adenomatous polyposis syndromes, intestinal hamartomas, intestinal pseudo-obstruction, irritable bowel syndrome, ischemic colitis, juvenile polyposis, juvenile polyps, Klippel-Trénaunay-Weber syndrome, leiomyomas,

lipomas, lymphocytic (microscopic) colitis, lymphoid hyperplasia and lymphoma, malaknock outplakia, malignant lymphoma, malignant neoplasms, malrotation, metastatic neoplasms, mixed hyperplastic and adenomatous polyps, mucosal prolapse syndrome, neonatal necrotizing enterocolitis, neuroendocrine cell tumors, neurogenic tumors, 5 neutropenic enterocolitis, non-neoplastic polyps, Peutz-Jeghers syndrome, pneumatosis cystoides intestinalis, polyposis coli, pseudomembranous colitis, pseudoxanthoma elasticum, pure squamous carcinomas, radiation colitis, schistosomiasis, Shigella colitis (bacillary dysentery), spindle cell carcinomas, spirochetosis, stercolar ulcers, stromal tumors, systemic sclerosis and CREST syndrome, trichuriasis, tubular adenoma 10 (adenomatous polyp, polypoid adenoma), Turcot's syndrome, Turner's syndrome, ulcerative colitis, villous adenoma, and volvulus.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 16.

15 In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 16.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially 20 identical to a polypeptide listed in Table 16.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 16.

In another aspect, the invention features a method of preventing or treating 25 cardiovascular disease, including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing cardiovascular disease, including administering to an animal (e.g., a human) a compound 30 that modulates the biological activity of a GPCR polypeptide substantially identical to a

polypeptide listed in Tables 17 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a cardiovascular disease or disorder. This method includes the steps of (a) providing a GPCR polypeptide
5 substantially identical to a polypeptide listed in Tables 17 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a cardiovascular disease or disorder. The GPCR polypeptide
10 can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a cardiovascular disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding
15 a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be
20 useful for the treatment of a cardiovascular disease or disorder.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a cardiovascular disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR
25 polypeptide substantially identical to a polypeptide listed in Tables 17 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be
30 useful for the treatment of a cardiovascular disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a cardiovascular disease or disorder. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 17 and 33, the
5 promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a cardiovascular disease or disorder.

10 In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a cardiovascular disease or disorder. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate
15 compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a cardiovascular disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a cardiovascular disease
20 or disorder. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment
25 of a cardiovascular disease or disorder. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder. The method includes the step of determining whether the patient has a mutation in a gene encoding a
30 polypeptide listed in Tables 17 and 33, wherein presence of the mutation indicates that the

patient may have an increased risk for developing a cardiovascular disease or disorder.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder. This method includes the step of determining whether the patient has a polymorphism in a gene
5 encoding a polypeptide listed in Tables 17 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a cardiovascular disease or disorder.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the
10 polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 17 and 33, wherein increased or
15 decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a cardiovascular disease or disorder.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder. The method includes the step of measuring the patient's expression levels of a polypeptide
20 listed in Tables 17 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a cardiovascular disease or disorder. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

One preferred cardiovascular disease that can be treated or diagnosed using the
25 methods of the invention or for which candidate therapeutic compounds may be identified is coronary artery disease. Others include acute coronary syndrome, acute idiopathic pericarditis, acute rheumatic fever, American trypanosomiasis (Chagas' disease), angina pectoris, ankylosing spondylitis, anomalous pulmonary venous connection, anomalous pulmonary venous drainage, aortic atresia, aortic regurgitation, aortic stenosis, aortic valve
30 insufficiency, aortopulmonary septal defect, asymmetric septal hypertrophy, asystole, atrial

fibrillation, atrial flutter, atrial septal defect, atrioventricular septal defect, autoimmune myocarditis, bacterial endocarditis, calcific aortic stenosis, calcification of the aortic valve, calcification of the valve ring, carcinoid heart disease, cardiac amyloidosis, cardiac arrest, cardiac arrhythmia, cardiac failure, cardiac myxoma, cardiac rejection, cardiac tamponade, cardiogenic shock, cardiomyopathy of pregnancy, chronic adhesive pericarditis, chronic constrictive pericarditis, chronic left ventricular failure, coarctation of the aorta, complete heart block, complete transposition of the great vessels, congenital bicuspid aortic valves, congenital narrowing of the left ventricular outflow tract, congenital pulmonary valve stenosis, congenitally corrected transposition of the great arteries, congestive heart failure, constrictive pericarditis, cor pulmonale, coronary artery origin from pulmonary artery, coronary atherosclerosis, dilated (congestive) cardiomyopathy, diphtheria, double inlet left ventricle, double outlet right ventricle, Ebstein's malformation, endocardial fibroelastosis, endocarditis, endomyocardial fibrosis, eosinophilic endomyocardial disease (Löffler endocarditis), fibroma, glycogen storage diseases, hemochromatosis, hypertensive heart disease, hyperthyroid heart disease, hypertrophic cardiomyopathy, hypothyroid heart disease, idiopathic dilated cardiomyopathy, idiopathic myocarditis, infectious myocarditis, infective endocarditis, ischemic heart disease, left ventricular failure, Libman-Sachs endocarditis, lupus erythematosus, Lyme disease, marantic endocarditis, metastatic tumors, mitral insufficiency, mitral regurgitation, mitral stenosis, mitral valve prolapse, mucopolysaccharidoses, multifocal atrial tachycardia, myocardial infarction, myocardial ischemia, myocardial rupture, myocarditis, myxomatous degeneration, nonatheromatous coronary artery disease, nonbacterial thrombotic endocarditis, noninfectious acute pericarditis, nonviral infectious pericarditis, obliterative cardiomyopathy, patent ductus arteriosus, pericardial effusion, pericardial tumors, pericarditis, persistent truncus arteriosus, premature ventricular contraction, progressive infarction, pulmonary atresia with intact ventricular septum, pulmonary atresia with ventricular septal defect, pulmonary insufficiency, pulmonary regurgitation, pulmonary stenosis, pulmonary valve lesions, pulmonary valve stenosis, pyogenic pericarditis, Q fever, radiation-induced myocarditis, restrictive cardiomyopathy, rhabdomyoma, rheumatic aortic stenosis, rheumatic heart disease, Rocky Mountain spotted fever, rupture of the aortic valve, sarcoid myocarditis, scleroderma,

shingolipidoses, sinus brachycardia, sudden death syndrome, syphilis, systemic embolism from mural thrombi, systemic lupus erythematosus, tetralogy of fallot, thiamine deficiency (Beriberi) heart disease, thoracic outlet syndrome, Torsade de Pointes, toxic cardiomyopathy, toxic myocarditis, toxoplasmosis, trichinosis, tricuspid atresia, tricuspid insufficiency, tricuspid regurgitation, tricuspid stenosis, tricuspid valve lesions, tuberculo-
5 pericarditis, typhus, ventricular aneurysm, ventricular fibrillation, ventricular septal defect, ventricular tachycardia, ventriculoarterial septal defect, viral pericarditis, and Wolff-Parkinson-White syndrome.

In another aspect, the invention features a non-human mammal (e.g., a mouse),
10 having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 17.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 17.

15 In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 17.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to
20 a polypeptide listed in Table 17.

In another aspect, the invention features a method of preventing or treating a disease of the intestine including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, operably linked to a promoter.

25 In still another aspect, the invention features a method of treating or preventing a disease of the intestine including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33.

In yet another aspect, the invention features a method for determining whether a
30 candidate compound is a compound that may be useful for the treatment of a disease or

disorder of the intestine. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the intestine. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the intestine. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the intestine.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the intestine. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the intestine.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the intestine. This method includes (a) providing a nucleic acid molecule comprising a

promoter from a gene encoding a GPCR polypeptide listed in Tables 18 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that
5 the candidate compound may be useful for the treatment of a disease or disorder of the intestine.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the intestine. This method includes the steps of: (a) providing a GPCR polypeptide
10 substantially identical to a polypeptide listed in Tables 18 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the intestine.

15 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the intestine. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an
20 alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the intestine. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient
25 has an increased risk for developing a disease or disorder of the intestine. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 18 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the intestine.

In a related aspect, the invention features another method for determining whether a
30 patient has an increased risk for developing a disease or disorder of the intestine. This

method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 18 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the intestine.

- 5 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

- In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the intestine. The
10 method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 18 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the intestine.

- In still another aspect, the invention features yet another method for determining
15 whether a patient has an increased risk for developing a disease or disorder of the intestine. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 18 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the intestine. Preferably, the expression levels are determined by measuring levels of
20 polypeptide or mRNA.

- Diseases of the intestine that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include abdominal hernia, abetalipoproteinemia, abnormal rotation, acute hypotensive hypoperfusion, acute intestinal ischemia, acute small intestinal infarction, adenocarcinoma,
25 adenoma, adhesions, amebiasis, anemia, arterial occlusion, atypical mycobacteriosis, bacterial diarrhea, bacterial overgrowth typeh syndromes, botulism, Campylobacter fetus infection, Campylobacter jejuni, carbohydrate absorption defects, carcinoid tumors, celiac disease (nontropical sprue, gluten-induced enteropathy), cholera, Crohn's disease, chronic intestinal ischemia, Clostridium difficile pseudomembranous enterocolitis, Clostridium
30 perfringens, congenital umbilical hernia, Cronkhite-Canada syndrome, cytomegalovirus

enterocolitis, diarrhea, diarrhea caused by invasive bacteria, diverticulitis, diverticulosis, dysentery, enteroinvasive and enterohemorrhagic *Escherichia coli* infection, eosinophilic gastroenteritis, failure of peristalsis, familial polyposis syndromes, food poisoning, fungal enteritis, gangliocytic paragangliomas, Gardner's syndrome, gastrointestinal stromal neoplasms, giardiasis, hemorrhoids, hernia, hyperplastic polyps, idiopathic inflammatory bowel disease, ileus, imperforate anus, intestinal (abdominal ischemia), intestinal atresia, intestinal cryptosporidiosis, microsporidiosis & isosporiasis in AIDS, intestinal hamartomas, intestinal helminthiasis, intestinal hemorrhage, intestinal infiltrative disorders, intestinal lymphangiectasia, intestinal obstruction, intestinal perforation, intestinal reduplication, intestinal stenosis, intestinal tuberculosis, intussusception, jejunal diverticulosis, juvenile polyposis, juvenile retention polyps, lactase deficiency, lymphomas, malabsorption syndrome, malignant lymphoma, malignant neoplasms, malrotations, mechanical obstruction, Meckel's diverticulum, meconium ileus, mediterranean lymphoma, mesenchymal tumors, mesenteric vasculitis, mesenteric vein thrombosis, metastatic neoplasms, microvillus inclusion disease, mixed hyperplastic and adenomatous polyps, neonatal necrotizing enterocolitis, nodular duodenum, nonocclusive intestinal ischemia, nonspecific duodenitis, nontyphoidal salmonellosis, omphalocele, parasitic infections, peptic ulcer disease, Peutz-Jeghers syndrome, pneumatosis cystoides intestinalis, poorly differentiated neuroendocrine carcinomas, primary lymphoma, protein-losing enteropathy, *Salmonella* gastroenteritis, sarcoidosis, sarcomas, shigellosis, staphylococcal food poisoning, steatorrhea, sugar intolerance, thrombosis of the mesenteric veins, toxigenic diarrhea, toxigenic *Escherichia coli* infection, tropical sprue, tubular adenoma (adenomatous polyp, polypoid adenoma), typhoid fever, ulcers, vascular malformations, villous adenoma, viral enteritis, viral gastroenteritis, visceral myopathy, visceral neuropathy, vitelline duct remnants, volvulus, Western-type intestinal lymphoma, Whipple's disease (intestinal lipopystrophy), *Yersinia enterocolitica* & *Yersinia pseudotuberculosis* infection, and Zollinger-Ellison syndrome.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 18.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 18.

5 In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 18.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 18.

10 In another aspect, the invention features a method of preventing or treating a disease of the kidney including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33, operably linked to a promoter.

15 In still another aspect, the invention features a method of treating or preventing a disease of the kidney including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33.

20 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the kidney. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may
25 be useful for the treatment of a disease or disorder of the kidney. The GPCR polypeptide can be in a cell or in a cell-free assay system.

30 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the kidney. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule

encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the kidney.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the kidney. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the kidney.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the kidney. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 19 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the kidney.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the kidney. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the

polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the kidney.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the kidney. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the kidney. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 19 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the kidney.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 19 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the kidney.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 19 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the

patient may have an increased risk for developing a disease or disorder of the kidney.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney. The method includes the step of measuring the patient's expression levels of a polypeptide
5 listed in Tables 19 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the kidney. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the kidney that can be treated or diagnosed using the methods of the
10 invention or for which candidate therapeutic compounds may be identified include acquired cystic disease, acute (postinfectious) glomerulonephritis, acute infectious interstitial nephritis, acute interstitial nephritis, acute pyelonephritis, acute renal failure, acute transplant failure, acute tubular necrosis, adult polycystic kidney disease, AL amyloid, analgesic nephropathy, anti-glomerular basement membrane disease (Goodpasture's
15 Syndrome), asymptomatic hematuria, asymptomatic proteinuria, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, Bence Jones cast nephropathy, benign familial hematuria, benign nephrosclerosis and atheromatous embolization, bilateral cortical necrosis, chronic glomerulonephritis, chronic interstitial nephritis, chronic pyelonephritis, chronic renal failure, chronic transplant failure, circulating
20 immune complex nephritis, crescentic glomerulonephritis, cryoglobulinemia, cystic renal dysplasia, diabetic glomerulosclerosis, diabetic nephropathy, dialysis cystic disease, drug induced (allergic) acute interstitial nephritis, ectopic kidney, Fabry's disease, familial juvenile nephronophthisis-medullary cystic disease complex, focal glomerulosclerosis (segmental hyalinosis), glomerulocystic disease, glomerulonephritis, glomerulonephritis
25 associated with bacterial endocarditis, glomerulosclerosis, hemolytic-uremic syndrome, Henoch-Schönlein purpura, hepatitis-associated glomerulonephritis, hereditary nephritis (Alport syndrome), horseshoe kidney, hydronephrosis, IgA nephropathy, infantile polycystic kidney disease, ischemic acute tubular necrosis, light-chain deposit disease, malignant nephrosclerosis, medullary cystic disease, membranoproliferative
30 (mesangiocapillary) glomerulonephritis, membranous glomerulonephritis, membranous

nephropathy, mesangial proliferative glomerulonephritis (includes Berger's Disease), minimal change glomerular disease, minimal change nephrotic syndrome, nephritic syndrome, nephroblastoma (Wilms tumor), nephronophthisis (medullary cystic disease complex), nephrotic syndrome, plasma cell dyscrasias (monoclonal immunoglobulin-induced renal damage), polyarteritis nodosa, proteinuria, pyelonephritis, rapidly progressive (crescentic) glomerulonephritis, renal agenesis, renal amyloidosis, renal cell carcinoma, renal dysgenesis, renal dysplasia, renal hypoplasia, renal infection, renal osteodystrophy, renal stones (urolithiasis), renal tubular acidosis, renal vasculitis, renovascular hypertension, scleroderma (progressive systemic sclerosis), secondary acquired glomerulonephritis, simple renal cysts, systemic lupus erythematosus, thin basement membrane nephropathy, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, toxic acute tubular necrosis, tubular defects, tubulointerstitial disease in multiple myeloma, urate nephropathy, urinary obstruction, and vasculitis.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 19.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 19.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 19.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 19.

In another aspect, the invention features a method of preventing or treating a disease of the liver including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a

disease of the liver including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the liver. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the liver. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the liver. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the liver.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the liver. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human

mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the liver.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the liver. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 20 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the liver.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the liver. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the liver.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the liver. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the liver. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the liver. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 20 and 33, wherein presence of the mutation indicates that the patient may

have an increased risk for developing a disease or disorder of the liver.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the liver. This method includes the step of determining whether the patient has a polymorphism in a gene encoding
5 a polypeptide listed in Tables 20 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the liver.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

10 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the liver. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 20 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the
15 patient may have an increased risk for developing a disease or disorder of the liver.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the liver. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 20 and 33, wherein altered levels in the expression, relative to normal, indicate
20 that the patient has an increased risk for developing a disease or disorder of the liver. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the liver that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include acute
25 alcoholic hepatitis (acute sclerosing hyaline necrosis of the liver), acute graft-versus-host disease, acute hepatitis, acute hepatocellular injury associated with infectious diseases other than viral hepatitis, acute liver failure, acute viral hepatitis, adenovirus hepatitis, Alagille syndrome, alcoholic cirrhosis, alcoholic hepatitis, alcoholic liver disease, alpha1-antitrypsin deficiency, amebic abscess, angiolmyolipoma, angiosarcoma, ascending cholangitis,
30 autoimmune chronic active hepatitis (lupoid hepatitis), bile duct adenoma, bile duct

cystadenocarcinoma, bile duct cystadenoma, biliary atresia, biliary cirrhosis, biliary
 papillomatosis, bridging necrosis, Budd-Chiari syndrome, Byler disease, cardiac fibrosis of
 the liver, Caroli disease, cavernous hemangioma, cholangiocarcinoma, cholangitic abscess,
 cholestasis, cholestatic viral hepatitis, chronic active hepatitis, chronic alcoholic liver
 5 disease, chronic graft-versus-host disease, chronic hepatic venous congestion, chronic
 hepatitis, chronic liver failure, chronic passive congestion, chronic viral hepatitis, cirrhosis,
 combined hepatocellular and cholangiocarcinoma, confluent hepatic necrosis, congenital
 hepatic fibrosis, Crigler-Najjar syndrome, cryptogenic cirrhosis, cystic fibrosis, defects of
 coagulation, delta hepatitis, Dubin-Johnson syndrome, epithelioid hemangioendothelioma,
 10 erythrohepatic protoporphyria, extrahepatic biliary obstruction (primary biliary cirrhosis),
 fatty change, fatty liver, focal necrosis, focal nodular hyperplasia, fulminant viral hepatitis,
 galactosemia, Gilbert's syndrome, glycogen storage diseases, graft-versus-host disease,
 granulomatous hepatitis, hemangioma, hemangiosarcoma, hemochromatosis, hepatic
 adenoma, hepatic amebiasis, hepatic encephalopathy, hepatic failure, hepatic
 15 schistosomiasis, hepatic veno-occlusive disease, hepatitis A, hepatitis B, hepatitis C,
 hepatitis D, hepatitis E, hepatoblastoma, hepatocellular adenoma, hepatocellular carcinoma,
 hepatocellular necrosis, hepatorenal syndrome, hereditary fructose intolerance, hereditary
 hemochromatosis, herpesvirus hepatitis, hydatid cyst, hyperplastic lesions,
 hypoalbuminemia, infantile hemangioendothelioma, infarction of the liver, infectious
 20 mononucleosis hepatitis, inflammatory pseudotumor of the liver, intrahepatic
 cholangiocarcinoma, intrahepatic cholestasis, intrahepatic portal hypertension, ischemic
 necrosis (ischemic hepatitis), isoniazid-induced necrosis, jaundice, leptospirosis, liver cell
 adenoma, liver manifestations of Rocky Mountain spotted fever, macronodular cirrhosis,
 macrovesicular steatosis, malignant vascular neoplasms, mass lesions, massive hepatocellular
 25 necrosis, massive necrosis, mesenchymal hamartoma, metastatic tumors, micronodular
 cirrhosis, microvesicular steatosis, neonatal (physiologic) jaundice, neonatal hepatitis,
 neoplastic lesions, nodular transformation (nodular regenerative hyperplasia,
 nonsuppurative infections, nutritional cirrhosis, nutritional liver disease, oriental
 cholangiohepatitis, parasitic infestation of the liver, peliosis hepatis, porphyria cutaneo
 30 tarda, portal hypertension, portal vein thrombosis, posthepatic portal hypertension,

predictable (dose-related) toxicity, prehepatic portal hypertension, primary biliary cirrhosis, primary sclerosing cholangitis, pyogenic liver abscess, Q-fever hepatitis, Rotor's syndrome, sclerosing bile duct adenoma, sclerosing cholangitis, secondary hemochromatosis, submassive necrosis, syphilis, toxic liver injury, tyrosinemia, undifferentiated sarcoma, unpredictable (idiosyncratic) toxicity, vascular lesions, virus-induced cirrhosis, Wilson's disease, and zonal necrosis.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 20.

10 In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 20.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 20.

15 In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 20.

In another aspect, the invention features a method of preventing or treating lung disease, including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, operably linked to a promoter.

20 In still another aspect, the invention features a method of treating or preventing lung disease, including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33.

25 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a lung disease or disorder. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33; (b) contacting the GPCR polypeptide

30

with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a lung disease or disorder. The GPCR polypeptide can be in a cell or in a
5 cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the lung. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule
10 encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a
15 disease or disorder of the lung.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the lung. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR
20 polypeptide substantially identical to a polypeptide listed in Tables 21 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a
25 disease or disorder of the lung.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a lung disease or disorder. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 21 and 33, the
30 promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with

the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a lung disease or disorder.

5 In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a lung disease or disorder. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may
10 be useful for the treatment of a lung disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a lung disease or disorder. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33; (b) contacting the polypeptide with the candidate
15 compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a lung disease or disorder. Preferably, the GPCR polypeptide is in a cell or a cell free assay system.

20 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a lung disease or disorder. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 21 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a lung disease or disorder.

25 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a lung disease or disorder. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 21 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a lung disease or disorder.

30 In either of these two methods, the mutation or polymorphism is preferably

associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a lung disease or disorder. The method includes
5 measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 21 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a lung disease or disorder.

In still another aspect, the invention features yet another method for determining
10 whether a patient has an increased risk for developing a lung disease or disorder. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 21 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a lung disease or disorder. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

15 Preferred lung diseases (including those of the traches) that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include abnormal diffusion, abnormal perfusion, abnormal ventilation, accelerated silicosis, actinomycosis, acute air space pneumonia (acute bacterial pneumonia), acute bronchiolitis, acute congestion, acute infections of the lung, acute interstitial
20 pneumonia, acute necrotizing viral pneumonia, acute organic dust toxic syndrome, acute pneumonia, acute radiation pneumonitis, acute rheumatic fever, acute silicosis, acute tracheobronchitis, adenocarcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, adenovirus, adult respiratory distress syndrome (shock lung), agenesis, AIDS, air embolism, allergic bronchopulmonary mycosis, allergic granulomatosis and angiitis (Churg-Strauss),
25 allograft rejection, aluminum pneumoconiosis, alveolar microlithiasis, alveolar proteinosis, amebic lung abscess, amniotic fluid embolism, amyloidosis of the lung, anomalies of pulmonary vasculature, anomalous pulmonary venous return, apiration pneumonia, aplasia, asbestosis, asbestos-related diseases, aspergillosis, asthma, atelectasis, atriovenous fistulas, atypical mycobacterial infection, bacteremia, bacterial pneumonia, benign clear cell tumor,
30 benign epithelial tumors, benign fibrous mesothelioma, berylliosis, blastomycosis,

bronchial atresia, bronchial asthma, bronchial carcinoid tumor, bronchial isomerism,
 bronchial obstruction, bronchial stenosis, bronchiectasis, bronchiolalveolar carcinoma,
 bronchiolitis, bronchiolitis obliterans-organizing pneumonia, bronchocentric
 granulomatosis, bronchogenic cyst, bronchopneumonia, bronchopulmonary dysplasia,
 5 bronchopulmonary sequestration, bullae, bullous emphysema, cancer, carcinoid tumors,
 carcinoma of the lung (bronchogenic carcinoma), central (bronchogenic) carcinoma, central
 cyanosis, centriacinar emphysema, centrilobular emphysema, chest pain, Chlamydial
 pneumonia, chondroid hamartoma, chronic airflow obstruction, chronic bronchitis, chronic
 diffuse interstitial lung disease, chronic idiopathic pulmonary fibrosis, chronic lung abscess,
 10 chronic obstructive pulmonary diseases, chronic radiation pneumonitis, chronic silicosis,
 chylothorax, ciliary dyskinesia, coal worker's pneumoconiosis (anthracosis),
 coccidioidomycosis, collagen-vascular diseases, common cold, compensatory emphysema,
 congenital acinar dysplasia, congenital alveolar capillary dysplasia, congenital
 bronchobiliary fistula, congenital bronchoesophageal fistula, congenital cystic adenomatoid
 15 malformation, congenital pulmonary lymphangiectasis, congenital pulmonary overinflation
 (congenital emphysema), congestion, cough, cryptococcosis, cyanosis, cystic fibrosis,
 cysticercosis, cytomegalovirus, desquamative interstitial pneumonitis, destructive lung
 disease, diatomaceous earth pneumoconiosis, diffuse alveolar damage, diffuse pulmonary
 hemorrhage, diffuse septal amyloidosis, diffuse panbronchiolitis, *Dirofilaria immitis*,
 20 diseases of the pleura, distal acinar (paraseptal) emphysema, drug-induced asthma, drug-
 induced diffuse alveolar damage, dyspnea, ectopic hormone syndromes, emphysema,
 empyema, eosinophilic pneumonias, exercise-induced asthma, extralobar sequestration,
 extrinsic allergic asthma, fat emboli, focal dust emphysema, follicular bronchiolitis,
 follicular bronchitis, foreign-body embolism, Fuller's earth pneumoconiosis, functional
 25 resistance to arterial flow (vasoconstriction), fungal granulomas of the lung, fungal
 infections, Goodpasture's syndrome, graphite pneumoconiosis, gray hepatization,
 hamartomas, hard metal disease, hemoptysis, hemothorax, herniation of lung tissue, herpes
 simplex, heterotopic tissues, high-altitude pulmonary edema, histoplasmosis, horseshoe
 lung, humidifier fever, hyaline membrane disease, hydatid cysts, hydrothorax,
 30 hypersensitivity pneumonitis (extrinsic allergic alveolitis), hypoxic vascular remodeling,

iatrogenic drug-, chemical-, or radiation-induced interstitial fibrosis, idiopathic interstitial pneumonia, idiopathic organizing pneumonia, idiopathic pulmonary fibrosis (fibrosing alveolitis, Hamman-Rich syndrome, acute interstitial pneumonia), idiopathic pulmonary hemosiderosis, immunologic interstitial fibrosis, immunologic interstitial pneumonitis, 5 immunologic lung disease, infections causing chronic granulomatous inflammation, infections causing chronic suppurative inflammation, infections of the air passages, infiltrative lung disease, inflammatory lesions, inflammatory pseudotumors, influenza, interstitial diseases of uncertain etiology, interstitial lung disease, interstitial pneumonitis in connective tissue diseases, intralobar sequestration of the lung (congenital), intrinsic 10 (nonallergic) asthma, invasive pulmonary aspergillosis, kaolin pneumoconiosis, Kartagener's syndrome, Klebsiella pneumonia, Langerhans' cell histiocytosis (histiocytosis X), large cell undifferentiated carcinoma, larval migration of *Ascaris lumbricoides*, larval migration of *Strongyloides stercoralis*, left pulmonary artery "sling", Legionella pneumonia, lipid pneumonia, lobar pneumonia, localized emphysema, long-standing bronchial obstruction, 15 lung abscess, lung collapse, lung fluke, lung transplantation implantation response, lymphangiomyomatosis, lymphocytic interstitial pneumonitis (pseudolymphoma, lymphoma, lymphomatoid granulomatosis, malignant mesothelioma, massive pulmonary hemorrhage in the newborn, measles, meconium aspiration syndrome, mesenchymal cystic hamartomas, mesenchymal tumors, mesothelioma, metal-induced lung diseases, metastatic calcification, metastatic neoplasms, metastatic ossification, mica pneumoconiosis, mixed 20 dust fibrosis, mixed epithelial-mesenchymal tumors, mixed type neoplasms, mucoepidermoid tumor, mucoviscidosis (fibrocystic disease of the pancreas), mycoplasma pneumoniae, necrotizing bacterial pneumonia, necrotizing sarcoid granulomatosis, neonatal respiratory distress syndrome, neoplasms of the pleura, neuromuscular syndromes, 25 nocardiosis, nondestructive lung disease, North American blastomycosis, occupational asthma, organic dust disease, panacinar emphysema, Pancoast's syndrome, paracoccidioidomycosis, parainfluenza, paraneoplastic syndromes, paraseptal emphysema (paracicatricial), parasilicosis syndromes, parasitic infections of the lung, peripheral cyanosis, peripheral lung carcinoma, persistent pulmonary hypertension of the newborn, 30 pleural diseases, pleural effusion, pleural plaques, pneumococcal pneumonia,

pneumoconioses (inorganic dust diseases), Pneumocystis carinii pneumonia,
 pneumocystosis, pneumonitis, pneumothorax, precapillary pulmonary hypertension,
 primary (childhood) tuberculosis, primary (idiopathic) pulmonary hypertension, primary
 mesothelial neoplasms, primary pulmonary hypertensions, progressive massive fibrosis,
 5 psittacosis, pulmonary actinomycosis, pulmonary air-leak syndromes, pulmonary alveolar
 proteinosis, pulmonary arteriovenous malformation, pulmonary blastoma, pulmonary
 capillary hemangiomatosis, pulmonary carcinosarcoma, pulmonary edema, pulmonary
 embolism, pulmonary eosinophilia, pulmonary fibrosis, pulmonary hypertension,
 pulmonary hypoplasia, pulmonary infarction, pulmonary infiltration and eosinophilia,
 10 pulmonary interstitial air (pulmonary interstitial emphysema), pulmonary lesions,
 pulmonary nocardiosis, pulmonary parenchymal anomalies, pulmonary thromboembolism,
 pulmonary tuberculosis, pulmonary vascular disorders, pulmonary vasculitides, pulmonary
 veno-occlusive disease, pyothorax, radiation pneumonitis, recurrent pulmonary emboli, red
 hepatization, respiration failure, respiratory syncytial virus, Reye's syndrome, rheumatoid
 15 lung disease, Rickettsial pneumonia, rupture of pulmonary arteries, sarcoidosis, scar cancer,
 scimitar syndrome, scleroderma, sclerosing hemangioma, secondary (adult) tuberculosis,
 secondary bacterial pneumonia, secondary pleural neoplasms, secondary pulmonary
 hypertension, senile emphysema, siderosis, silicate pneumoconiosis asbestosis, silicosis,
 silicosis, simple nodular silicosis, Sjögren's syndrome, small airway lesions, small cell
 20 carcinoma, small cell undifferentiated (oat cell) carcinoma, spontaneous pneumothorax,
 sporotrichosis, sputum production, squamous (epidermoid) carcinoma, stannosis,
 staphylococcal pneumonia, suppuration (abscess formation), systemic lupus erythematosus,
 talcosis, tension pneumothorax, tracheal agenesis, tracheal stenosis, tracheobronchial
 amyloidosis, tracheobronchomegaly, tracheoesophageal fistula, transient tachypnea of the
 25 newborn (neonatal wet lung), tungsten carbide pneumoconiosis, usual interstitial
 pneumonia, usual interstitial pneumonitis, varicella, viral pneumonia, visceral pleural
 thickening, Wegener's granulomatosis, and whooping cough (pertussis).

In another aspect, the invention features a non-human mammal (e.g., a mouse),
 having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide
 30 substantially identical to a polypeptide listed in Table 21.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 21.

5 In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 21.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 21.

10 In another aspect, the invention features a method of preventing or treating muscular disease, including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, operably linked to a promoter.

15 In still another aspect, the invention features a method of treating or preventing muscular disease, including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33.

20 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a muscular disease or disorder. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may
25 be useful for the treatment of a muscular disease or disorder. The GPCR polypeptide can be in a cell or in a cell-free assay system.

30 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a muscular disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding

a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a muscular disease or disorder.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a muscular disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a muscular disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a muscular disease or disorder. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 22 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a muscular disease or disorder.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a muscular disease or disorder. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate

compound may be useful for the treatment of a muscular disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a muscular disease or disorder. This method includes (a) providing a GPCR polypeptide substantially identical to
5 a polypeptide listed in Tables 22 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a muscular disease or disorder. Preferably the GPCR polypeptide is in a cell or a cell free
10 assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a muscular disease or disorder. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 22 and 33, wherein presence of the mutation indicates that the patient may
15 have an increased risk for developing a muscular disease or disorder.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a muscular disease or disorder. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 22 and 33, wherein presence of the polymorphism indicates
20 that the patient may have an increased risk for developing a muscular disease or disorder.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a
25 patient has an increased risk for developing a muscular disease or disorder. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 22 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a muscular disease or disorder.

30 In still another aspect, the invention features yet another method for determining

whether a patient has an increased risk for developing a muscular disease or disorder. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 22 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a muscular disease or disorder.

- 5 Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Preferred muscular diseases that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include abnormalities of ion channel closure, acetylcholine receptor deficiency, acetylcholinesterase
10 deficiency, acid maltase deficiencies (type 2 glycogenosis), acquired myopathies, acquired myotonia, adult myotonic dystrophy, alveolar rhabdomyosarcoma, aminoglycoside drugs, amyloidosis, amyotrophic lateral sclerosis, antimyelin antibodies, bacteremic myositis, Batten's disease (neuronal ceroid lipofuscinoses), Becker's muscular dystrophy, benign neoplasms, Bornholm disease, botulism, branching enzyme deficiency (type 4
15 glycogenosis), carbohydrate storage diseases, carnitine deficiencies, carnitine palmitoyltransferase deficiency, central core disease, centronuclear (myotubular) myopathy, Chagas' disease, chondrodystrophic myotonia, chronic renal disease, congenital fiber type disproportion, congenital muscular dystrophy, congenital myopathies, congenital myotonic dystrophy, congenital paucity of synaptic clefts, cysticercosis, cytoplasmic body myopathy,
20 debranching enzyme deficiency (type 3 glycogenosis), defect in acetylcholine synthesis, denervation, dermatomyositis, diabetes mellitus, diphtheria, disorders of glycolysis, disorders of neuromuscular junction, distal muscular dystrophy, drug induced inflammatory myopathy, Duchenne muscular dystrophy, embryonal rhabdomyosarcoma, Emery-Dreifuss muscular dystrophy, exotoxic bacterial infections, facioscapulohumeral muscular dystrophy,
25 failure of neuromuscular transmission, fiber necrosis, fibromyalgia, fingerprint body myopathy, Forbe's disease, gas gangrene, Guillain-Barré syndrome, inclusion body myositis, infantile spinal muscular atrophies, infectious myositis, inflammatory myopathies, influenza, Isaac's syndrome, ischemia, Kearns-Sayre syndrome, lactase dehydrogenase deficiency, Lambert-Eaton syndrome, Leigh's disease, leuknock outdystrophies, limb girdle
30 muscular dystrophy, lipid storage myopathies, Luft's disease, lysosomal glycogen storage

disease with normal acid maltase activity, malignant neoplasms, malignant hyperthermia, McArdle's disease, MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokes), MERRF syndrome (myoclonus epilepsy with ragged-red fibers), metabolic myopathies, microfibrillar myopathy, mitochondrial myopathies, multicore disease (minicore disease), multisystem triglyceride storage disease, muscle wasting from diabetes, muscular dystrophies, myasthenia gravis, myasthenic syndrome (Eaton-Lambert syndrome), myoadenylate deaminase deficiency, myoglobinuria, myopathies, myophosphorylase deficiency (type 5 glycogenosis), myositis, myositis ossificans, myotonia congenita, myotonic muscular dystrophy, nemaline myopathy, ocular muscular dystrophy, oculopharyngeal muscular dystrophy, paramyotonia, parasitic myopathies, periodic paralysis, peripheral neuropathies, phosphofructokinase deficiency (type 7 glycogenosis), phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, pleomorphic rhabdomyosarcoma, polymyositis, Pompe's disease, progressive muscular atrophy, progressive systemic sclerosis, reducing body myopathy, Refsum's disease, rhabdomyolysis, rhabdomyoma, rhabdomyosarcoma, sarcoidosis, sarcoma botryoides, sarcotubular myopathy, secondary congenital myopathies, slow channel syndrome, spasmodic torticollis, spheroid body myopathy, spinal muscular atrophy, steroid myopathy, stiff-person syndrome, systemic lupus erythematosus, Tauri's disease, tick paralysis, toxic myopathies, toxoplasmosis, trichinosis, trilaminar fiber myopathy, type 2 myofiber atrophy, typhoid fever, vasculitis, viral myositis, and zebra body myopathy.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 22.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 22.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 22.

In another aspect, the invention features a cell from a non-human mammal having a

mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 22.

5 In another aspect, the invention features a method of preventing or treating a disease of the ovary including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a disease of the ovary including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a
10 polypeptide listed in Tables 23 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the ovary. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33; (b) contacting the GPCR
15 polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the ovary. The GPCR polypeptide can be in a cell or in a cell-free assay system.

20 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of disease or disorder of the ovary. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23
25 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the ovary.

30 In yet another aspect, the invention features a method for determining whether a

candidate compound is a compound that may be useful for the treatment of a disease or disorder of the ovary. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33; (b) 5 contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the ovary.

10 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the ovary. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 23 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with 15 the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the ovary.

In another aspect, the invention features yet another method for determining whether 20 a candidate compound may be useful for the treatment of a disease or disorder of the ovary. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate 25 compound may be useful for the treatment of a disease or disorder of the ovary.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the ovary. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33; (b) contacting the polypeptide with the 30 candidate compound; and (c) measuring the half-life of the polypeptide, wherein an

alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the ovary. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

5 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the ovary. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 23 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the ovary.

10 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the ovary. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 23 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the ovary.

15 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the ovary. The method
20 includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 23 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the ovary.

 In still another aspect, the invention features yet another method for determining
25 whether a patient has an increased risk for developing a disease or disorder of the ovary. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 23 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the ovary. Preferably, the expression levels are determined by measuring levels of polypeptide
30 or mRNA.

Diseases of the ovary that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include autoimmune oophoritis, brenner tumors, choriocarcinoma, clear cell adenocarcinoma, clear cell carcinoma, corpus luteal cysts, decidual reaction, dysgerminoma, embryonal carcinoma, 5 endometrioid tumors, endometriosis, endometriotic cysts, epithelial inclusion cysts, fibrothecoma, follicular cysts, gonadoblastoma, granulosa-stroma cell tumors, granulosa-theca cell tumor, gynandroblastoma, hilum cell hyperplasia, luteal cysts, luteal hematomas, luteoma of pregnancy, massive ovarian edema, metastatic neoplasm, mixed germ cell tumors, monodermal tumors, mucinous tumors, neoplastic cysts, ovarian changes secondary 10 to cytotoxic drugs and radiation, ovarian fibroma, polycystic ovary syndrome, pregnancy luteoma, premature follicle depletion, pseudomyxoma peritonei, resistant ovary, serous tumors, Sertoli-Leydig cell tumor, sex-cord tumor with annular tubules, steroid (lipid) cell tumor, stromal hyperplasia, stromal hyperthecosis, teratoma, theca lutein cysts, thecomas, transitional cell carcinoma, undifferentiated carcinoma, and yolk sac carcinoma 15 (endodermal sinus tumor).

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 23.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), 20 having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 23.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 23.

25 In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 23.

In another aspect, the invention features a method of preventing or treating blood disease, including introducing into a human an expression vector that includes a nucleic 30 acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed

in Tables 24 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing blood disease, including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a blood disease or disorder. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a blood disease or disorder. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a blood disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a blood disease or disorder.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a blood disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c)

measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a blood disease or disorder.

5 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a blood disease or disorder. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 24 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with
10 the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a blood disease or disorder.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a blood disease or disorder. This
15 method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a blood disease or disorder.

20 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a blood disease or disorder. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the
25 half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a blood disease or disorder. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient
30 has an increased risk for developing a blood disease or disorder. The method includes the

step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 24 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a blood disease or disorder.

5 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a blood disease or disorder. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 24 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a blood disease or disorder.

10 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a blood disease or disorder. The method includes measuring biological activity of a GPCR polypeptide from the patient that is
15 substantially identical to a polypeptide listed in Tables 24 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a blood disease or disorder.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a blood disease or disorder. The
20 method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 24 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a blood disease or disorder. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Preferred blood diseases that can be treated or diagnosed using the methods of the
25 invention or for which candidate therapeutic compounds may be identified include abnormal hemoglobins, abnormalities in granulocyte count, abnormalities in lymphocyte count, abnormalities in monocyte count, abnormalities of blood platelets, abnormalities of platelet function, acanthocytosis, acquired neutropenia, acute granulocytic leukemia, acute idiopathic thrombocytopenic purpura, acute infections, acute lymphoblastic leukemia, acute
30 lymphocytic leukemia, acute myeloblastic leukemia, acute myelocytic leukemia, acute

myeloid leukemia, acute pyogenic bacterial infections, acute red cell aplasia, acute response to endotoxin, adult T-cell leukemia/lymphoma, afibrinogenemia, alpha thalassemia, altered affinity of hemoglobin for oxygen, amyloidosis, anemia, anemia due to acute blood loss, anemia due to chronic blood loss, anemia of chronic disease, anemia of chronic renal

5 failure, anemias associated with enzyme deficiencies, anemias associated with erythrocyte cytoskeletal defects, anemias caused by inherited disorders of hemoglobin synthesis, angiogenic myeloid metaplasia, aplastic anemia, ataxia-telangiectasia, Auer rods, autoimmune hemolytic anemias, B-cell chronic lymphocytic leukemia, B-cell chronic lymphoproliferative disorders, Bernard-Soulier disease, beta thalassemia, Blackfan-

10 Diamond disease, brucellosis, Burkitt's lymphoma, Chédiak-Higashi syndrome, cholera, chronic acquired pure red cell aplasia, chronic granulocytic leukemia, chronic granulomatous disease, chronic idiopathic myelofibrosis, chronic idiopathic thrombocytopenic purpura, chronic lymphocytic leukemia, chronic lymphoproliferative disorders, chronic myelocytic leukemia, chronic myelogenous leukemia, chronic myeloid

15 leukemia, chronic myeloproliferative disorders, congenital dyserythropoietic anemias, congenital dysfibrinogenemia, congenital neutropenia, corticosteroids, cyclic neutropenia, cytoplasmic maturation defect, deficiency of coagulation factors, delta-beta thalassemia, diphtheria, disorders of blood coagulation, disseminated intravascular coagulation & fibrinolysis, Döhle bodies, drug & chemical-induced hemolysis, drug-induced

20 thrombocytopenia, drugs that suppress granulopoiesis, E. coli, early preleukemic myeloid leukemia, eosinophilia, eosinophilic granuloma, erythrocyte enzyme deficiency, erythrocyte membrane defects, essential thrombocythemia, factor 7 deficiency, familial cyclic neutropenia, Felty's syndrome, fibrinolytic activity, folate antagonists, folic acid deficiency, Gaucher disease, Glanzmann's thrombasthenia, glucose-6-phosphate dehydrogenase

25 deficiency, granulated T-cell lymphocyte leukemia, granulocytic sarcoma, granulocytosis, Hageman trait, hairy cell leukemia (leukemic reticuloendotheliosis), Hand-Schüller-Christian disease, heavy-chain disease, hemoglobin C disease, hemoglobin constant spring, hemoglobin S, hemoglobinopathies, hemolysis caused by infectious agents, hemolytic anemia, hemolytic anemia secondary to mechanical erythrocyte destruction, hemolytic

30 blood transfusion reactions, hemolytic disease of the newborn, hemophagocytic disorders,

hemophilia A, hemophilia B (Christmas disease, factor 9 deficiency, hepatitis, hereditary elliptocytosis, hereditary spherocytosis, heterozygous beta thalassemia (Cooley's trait), homozygous beta thalassemia (Cooley's anemia), hypereosinophilic syndrome, hypoxia, idiopathic cold hemagglutinin disease, idiopathic thrombocytopenic purpura, idiopathic

5 warm autoimmune hemolytic anemia, immune drug induced hemolysis, immune-mediated hemolytic anemias, immunodeficiency disease, infantile neutropenia (Knock outstmann), instability of the hemoglobin molecule, iron deficiency anemia, isoimmune hemolytic anemia, juvenile chronic myeloid leukemia, Langerhans cell histiocytosis, large granular lymphocyte leukemia, lazy leukknock outcyte syndrome, Letterer-Siwe disease, leukemias,

10 leukemoid reaction, leukknock outerythroblastic anemia, lipid storage diseases, lymphoblastosis, lymphocytopenia, lymphocytosis, lymphoma, lymphopenia, macroangiopathic hemolytic anemia, malaria, marrow aplasia, May-Hegglin anomaly, measles, megaloblastic anemia, metabolic diseases, microangiopathic hemolytic anemia, microcytic anemia, miliary tuberculosis, mixed phenotupe acute leukemia, monoclonal

15 gammopathy of undetermined significance, monocytic leukemia, monocytosis, mucopolysaccharidosis, multiple myeloma, myeloblastic luekemia, myelodysplastic syndromes, myelofibrosis (agnogenic myeloid metaplasia), myeloproliferative diseases, myelosclerosis, neonatal thrombocytopenic purpura, neoplasms of hematopoietic cells, neutropenia, neutrophil dysfunction syndromes, neutrophil leukknock outcytosis,

20 neutrophilia, Niemann-Pick disease, nonimmune drug-induced hemolysis, normocytic anemia, nuclear maturation defects, parahemophilia, paroxysmal cold hemoglominuria, paroxysmal nocturnal hemoglobinuria, Pelger-Hüet anomaly, pernicious (Addisonian) anemia, plasma cell leukemia, plasma cell neoplasia, polycythemia, polycythemia rubra vera, presence of circulating anticoagulants, primary (idiopathic) thrombocythemia, primary

25 neoplasms, prolymphocytic leukemia, Proteus, Pseudomonas, pure red cell aplasia, pyogenic bacterial infection, pyruvate kinase deficiency, radiation, red cell aplasia, refractory anemias, ricketsial infections, Rosenthal's syndrome, secondary absolute polycythemia, septicemia, severe combined immunodeficiency disease, Sézary syndrome, sickle cell disease, sickle cell-beta thalassemia, sideroblastic anemia, solitary

30 plasmacytoma, storage pool disease, stress, structural hemoglobin variants, systemic lupus

erythematosis, systemic mastocytosis, tart cell, T-cell chronic lymphoproliferative disorders, T-cell prolymphocytic leukemia, thalassemias, thrombocytopenia, thrombotic thrombocytopenic purpura, toxic granulation, toxic granules in severe infection, typhus, vitamin B12 deficiency, vitamin K deficiency, Von Willebrand's disease, Waldenstrom
5 macroglobulinemia, and Wisknack outtt-aldrich syndrome.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 24.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse),
10 having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 24.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 24.

15 In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 24.

In another aspect, the invention features a method of preventing or treating a disease of the prostate including introducing into a human an expression vector that includes a
20 nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a disease of the prostate including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a
25 polypeptide listed in Tables 25 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the prostate. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33; (b)
30 contacting the GPCR polypeptide with the candidate compound; and (c) measuring

biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the prostate. The GPCR polypeptide can be in a cell or in a cell-free assay system.

5 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the prostate. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25
10 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the prostate.

15 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a blood disease or disorder of the prostate. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33; (b)
20 contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the prostate.

25 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the prostate. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 25 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with
30 the candidate compound; and (c) measuring reporter activity, wherein altered reporter

activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the prostate.

5 In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the prostate. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate
10 compound may be useful for the treatment of a disease or disorder of the prostate.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the prostate. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33; (b) contacting the polypeptide with the
15 candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the prostate. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

20 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 25 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the prostate.

25 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 25 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of
30 the prostate.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

5 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 25 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the prostate.

10 In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 25 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the prostate. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the prostate that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include acute bacterial prostatitis, acute prostatitis, adenoid basal cell tumor (adenoid cystic-like tumor),
20 allergic (eosinophilic) granulomatous prostatitis, atrophy, atypical adenomatous hyperplasia, atypical basal cell hyperplasia, basal cell adenoma, basal cell hyperplasia, BCG-induced granulomatous prostatitis, benign prostatic hyperplasia, benign prostatic hypertrophy, blue nevus, carcinosarcoma, chronic abacterial prostatitis, chronic bacterial prostatitis, cribriform hyperplasia, ductal (endometrioid) adenocarcinoma, granulomatous
25 prostatitis, hematuria, iatrogenic granulomatous prostatitis, idiopathic (nonspecific) granulous prostatitis, impotence, infectious granulomatous prostatitis, inflammatory pseudotumor, leiomyosarcoma, leukemia, lymphoepithelioma-like carcinoma, malaknock outplakia, malignant lymphoma, mucinous (colloid) carcinoma, nodular hyperplasia (benign prostatic hyperplasia), nonbacterial prostatitis, obstruction of urinary outflow, phyllodes
30 tumor, postatrophic hyperplasia, postirradiation granulomatous prostatitis, postoperative

spindle cell nodules, postsurgical granulomatous prostatitis, prostatic adenocarcinoma, prostatic carcinoma, prostatic intraepithelial neoplasia, prostatic melanosis, prostatic neoplasm, prostatitis, rhabdomyosarcoma, sarcomatoid carcinoma of the prostate, sclerosing adenosis, signet ring cell carcinoma, small-cell, undifferentiated carcinoma (high-grade
5 neuroendocrine carcinoma), squamous cell carcinoma of the prostate, stromal hyperplasia with atypia, transitional cell carcinoma of the prostate, xanthogranulomatous prostatitis, and xanthoma.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide
10 substantially identical to a polypeptide listed in Table 25.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 25.

In a related aspect, the invention features a cell from a non-human mammal having a
15 transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 25.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 25.

20 In another aspect, the invention features a method of preventing or treating skin disease, including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing skin
25 disease, including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a skin disease or
30 disorder. This method includes the steps of (a) providing a GPCR polypeptide substantially

identical to a polypeptide listed in Tables 26 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a skin disease or disorder. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a skin disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a skin disease or disorder

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a skin disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease skin disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a skin disease or disorder. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 26 and 33, the promoter operably linked

to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a skin disease or disorder.

5 In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a skin disease or disorder. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide.

10 Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a skin disease or disorder.

 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a skin disease or disorder. This method includes (a) providing a GPCR polypeptide substantially identical to a
15 polypeptide listed in Tables 26 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a skin disease or disorder. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

20 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a skin disease or disorder. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 26 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a skin disease or disorder.

25 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a skin disease or disorder. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 26 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a skin disease or disorder.

30 In either of these two methods, the mutation or polymorphism is preferably

associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a skin disease or disorder. The method includes
5 measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 26 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a skin disease or disorder.

In still another aspect, the invention features yet another method for determining
10 whether a patient has an increased risk for developing a skin disease or disorder. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 26 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a skin disease or disorder. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

15 Preferred skin diseases that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include acanthosis nigricans, acne vulgaris, acquired epidermolysis bullosa, acrochordons, acrodermatitis enteropathica, acropustulosis, actinic keratosis, acute cutaneous lupus erythematosus, age spots, allergic dermatitis, alopecia areata, angioedema, angiokeratoma,
20 angioma, anthrax, apocrine tumors, arthropid-bite reactions, atopic dermatitis, atypical fibroxanthoma, Bart's syndrome, basal cell carcinoma (basal cell epithelioma), Bateman's purpura, benign familial pemphigus (Hailey-Hailey disease), benign keratoses, Berloque dermatitis, blue nevus, borderline leprosy, Borrelia infection (lyme disease), Bowen's disease (carcinoma in situ), bullous pemphigoid, Café-au-lait spot, calcification, cellular
25 blue nevus, cellulitis, Chagas' disease, chickenpox (varicella), chloasma, chondrodermatitis nodularis helcis, chondroid syringoma, chronic actinic dermatitis, chronic cutaneous lupus erythematosus, chronic discoid lesions, cicatricial pemphigoid, collagen abnormalities, compound melanocytic nevus, congenital melanocytic nevus, connective tissue nevus, contact dermatitis, cutaneous leishmaniasis, cutis laxa, cysts of the skin, dandruff, Darier's
30 disease (keratosis follicularis), deep fungal infections, delayed-hypersensitivity reaction,

- dermal Spitz's nevus, dermatitis, dermatitis herpetiformis, dermatofibroma (cutaneous fibrous histiocytoma), dermatofibrosarcoma protuberans, dermatomyositis, dermatophyte infections, dermatophytid reactions, dermoid cyst, dermatropic rickettsial infections, dermatropic viral infections, desmoplastic melanoma, discoid lupus erythematosus,
- 5 dominant dystrophic epidermolysis bullosa, Dowling-Meara epidermolysis bullosa, dyshidrotic dermatitis, dysplastic nevi, eccrine tumors, ecthyma, eczema, elastic tissue abnormalities, elastosis perforans serpiginosa, eosinophilic fasciitis, eosinophilic folliculitis, ephelides (freckles), epidermal cysts, epidermolysis bullosa, epidermolysis bullosa simplex, epidermotropic T-cell lymphoma, epidermotropic viruses, erysipelas, erythema multiforme,
- 10 erythema nodosum, erythema nodosum leprosum, fibrotic disorders, fibrous tumors, follicular mucinosis, Fordyce's condition, fungal infections, genodermatoses, graft-versus-host disease, granuloma annulare, granulomatous vasculitis, Grover's disease, hair follicle infections, hair follicle tumors, hair loss, halo nevus, herpes simplex, herpes zoster (shingles), hidradenitis suppurativa, histiocytic lesions, HIV infections, hives, human
- 15 papilloma virus, hyperhydrosis, ichthyosis, idiopathic skin diseases, impetigo, incontinentia pigmenti, intraepidermal spongiotic vesicles and bullae, invasive malignant melanoma, invasive squamous cell carcinoma, junctional epidermolysis bullosa, junctional melanocytic nevus, juvenile xanthogranuloma, Kaposi's sarcoma, keloids, keratinocytic lesions, keratinocytic tumors, keratoacanthoma, keratoderma blennorrhagicum, keratosis pilaris,
- 20 leiomyoma, lentigo, lentigo maligna (Hutchinson's freckle), lepromatous leprosy, leprosy (Hansen's disease), leukocytoclastic vasculitis, lichen planus, lichen sclerosus et atrophicus, lichen simplex chronicus, lichen striatus, lichenoid disorders, lichenoid drug reactions, light eruptions, linear bullous IgA dermatitis, lipoma, Lucio's phenomenon, lupus erythematosus, lymphatic filariasis, lymphocytic vasculitis, lymphocytoma cutis, lymphoid
- 25 lesions, lymphomatoid papulosis, malignant blue nevus, malignant lymphomas, malignant melanoma, malignant melanoma in situ (noninvasive malignant melanoma), mast cell neoplasms, mastocytosis, measles, melanocyte disorders, melanocytic lesions, melanocytic neoplasms, melanocytic nevus, melanocytic nevus with dysplasia, melanotic macule, reactive type, melasma, merkel cell (neuroendocrine) carcinoma, metastatic melanoma,
- 30 miliaria, mixed connective tissue disease, molluscum contagiosum, morphea, mucin

deposition, mucocutaneous leishmaniasis, mycetoma, mycobacterial infection, Mycobacterium marinum, Mycobacterium ulcerans, mycosis fungoides (cutaneous T cell lymphoma), myxoid cyst, necrobiosis lipoidica, necrobiosis lipoidica diabetorum, necrolytic migratory erythema, necrotizing fasciitis, neoplasms of dermal mesenchymal cells, neoplasms of keratinocytes, neoplasms of skin appendages, neoplasms of the epidermis, neural tumors, neuroendocrine carcinoma of the skin, neurothekeoma, nevocellular nevus (melanocytic nevus), nummular dermatitis, obliterative vasculitis, onchocerciasis, Paget's disease, pale cell acanthoma of Degos, palisaded encapsulated neuroma, papillomavirus infections, paraneoplastic pemphigus, parasitic infections, pemphigoid gestationis, pemphigus, pemphigus foliaceus, pemphigus vulgaris, perivascular infiltrates, pilar cysts, pinta, pityriasis alba, pityriasis lichenoides chronica (of Juliusberg), pityriasis lichenoides et varioliformis acuta, pityriasis rosea, pityriasis rubra pilaris, plantar warts, porokeratosis, pressure necrosis, progressive systemic sclerosis, protozoal infections, pruritic urticarial papules and plaques of pregnancy, pruritis ani, pseudofolliculitis barbae, pseudoxanthoma elasticum, psoriasis vulgaris, pyogenic granuloma, radial growth type phase melanoma, recessive dystrophic epidermolysis bullosa, Reiter's syndrome, ringworm, Rochalimaea henselae infection, rosacea, rubella, sarcoidosis, scabies, Schamberg's disease, scleroderma, sebaceous hyperplasia, sebaceous tumors, seborrheic dermatitis, seborrheic keratosis, Sézary syndrome, skin manifestations of systemic diseases, small plaque parapsoriasis, smallpox (variola), solitary mastocytoma, spirochetal infections, Spitz's nevus, Spitz's nevus junctional type, squamous cell carcinoma, stasis dermatitis, Stevens-Johnson syndrome, subacute cutaneous lupus erythematosus, subcorneal pustular dermatosis, superficial fungal infections, superficial spreading melanoma in situ, syphilis, syringoma, systemic lupus erythematosus, systemic mastocytosis, tinea (dermatophytosis, tinea versicolor, toxic epidermal necrolysis, transient acantholytic dermatosis, tuberculoid leprosy, tuberculosis, urticaria, urticaria pigmentosa, urticarial vasculitis, vascular tumors, verruca vulgaris (common wart), vertical growth type phase melanoma, visceral leishmaniasis, vitiligo, warty dyskeratoma, Weber-Cockayne epidermolysis bullosa, Worringer-Knorr disease, xanthomas, xeroderma pigmentosum, xerosis, and yaws.

In another aspect, the invention features a non-human mammal (e.g., a mouse),

having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 26.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially
5 identical to a polypeptide listed in Table 26.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 26.

In another aspect, the invention features a cell from a non-human mammal having a
10 mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 26.

In another aspect, the invention features a method of preventing or treating a disease of the spleen including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide
15 listed in Tables 27 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a disease of the spleen including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33.

20 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the spleen. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the
25 GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the spleen. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a
30 candidate compound is a compound that may be useful for the treatment of a disease or

disorder of the spleen. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the spleen.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the spleen. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the spleen.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the spleen. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 27 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the spleen.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the spleen. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical

to a polypeptide listed in Tables 27 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the spleen.

5 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the spleen. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an
10 alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the spleen. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient
15 has an increased risk for developing a disease or disorder of the spleen. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 27 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the spleen.

In a related aspect, the invention features another method for determining whether a
20 patient has an increased risk for developing a disease or disorder of the spleen. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 27 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the spleen.

25 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the spleen. The method
30 includes measuring biological activity of a GPCR polypeptide from the patient that is

substantially identical to a polypeptide listed in Tables 27 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the spleen.

In still another aspect, the invention features yet another method for determining
5 whether a patient has an increased risk for developing a disease or disorder of the spleen. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 27 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the spleen. Preferably, the expression levels are determined by measuring levels of polypeptide
10 or mRNA.

Diseases of the spleen that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include abnormal immunoblastic proliferations of unknown origin, acute infections, acute parasitemias, agnogenic myeloid metaplasia, amyloidosis, angioimmunoblastic
15 lymphadenopathy, antibody-coated cells, asplenia, autoimmune diseases, autoimmune hemolytic anemias, B-cell chronic lymphocytic leukemia and prolymphocytic leukemia, babesiosis, bone marrow involvement by carcinoma, brucellosis, carcinoma, ceroid histiocytosis, chronic alcoholism, chronic granulomatous disease, chronic hemolytic anemias, chronic hemolytic disorders, chronic immunologic inflammatory disorders,
20 chronic infections, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic parasitemias, chronic uremia, cirrhosis, cold agglutinin disease, congestive splenomegaly, cryoglobulinemia, disseminated tuberculosis, dysproteinemias, endocrine disorders, erythroblastic leukemia, erythropoiesis, essential thrombocythemia, extramedullary hematopoiesis, Felty syndrome, fibrocongestive splenomegaly, fungal infections, gamm
25 heavy-chain disease, Gaucher's disease, graft rejection, granulomatous infiltration, hairy cell leukemia, hamartomas, Hand-Schüller-Christian disease, hemangiomas, hemangiosarcomas, hematologic disorders, hemoglobinopathies, hemolytic anemias, hereditary elliptocytosis, hereditary spherocytosis, histiocytic medullary reticulosis, histiocytosis X, Hodgkin's disease, hypersensitivity reactions, hypersplenism,
30 hyposplenism, idiopathic thrombocytopenic purpura, IgA deficiency, immune granulomas,

immune thrombocytopenia, immune thrombocytopenic purpura, immunodeficiency disorders, infection associated hemophagocytic syndrome, infectious granulomas, infectious mononucleosis, infective endocarditis, infiltrative splenomegaly, inflammatory pseudotumors, leishmaniasis, Leterer-Siwe disease, leukemia, lipogranulomas, lymphocytic leukemias, lymphoma, malabsorption syndromes, malaria, malignant lymphoma, megakaryoblastic leukemia, metastatic tumor, monocytic leukemias, mucopolysaccharidoses, multicentric Castleman's disease, multiple myeloma, myelocytic leukemias, myelofibrosis, myeloproliferative syndromes, neoplasms, Niemann-Pick disease, non-Hodgkin's lymphoma, parasitic disorders, parasitized red blood cells, peliosis, polycythemia rubra vera, portal vein congestion, portal vein stenosis, portal vein thrombosis, portal venous hypertension, rheumatoid arthritis, right-sided cardiac failure, sarcoidosis, sarcoma, secondary amyloidosis, secondary myeloid metaplasia, serum sickness, sickle-cell disease, splenic cysts, splenic infarction, splenic vein hypertension, splenic vein stenosis, splenic vein thrombosis, splenomegaly, storage diseases, systemic lupus erythematosus, systemic vasculitides, T-cell chronic lymphocytic leukemia, thalassemia, thrombocytopenic purpura, thyrotoxicosis, trapping of immature hematologic cells, tuberculosis, tumorlike conditions, typhoid fever, vascular tumors, vasculitis, and viral infections.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 27.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 27.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 27.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 27.

In another aspect, the invention features a method of preventing or treating a disease of the stomach including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, operably linked to a promoter.

5 In still another aspect, the invention features a method of treating or preventing a disease of the stomach including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33.

10 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the stomach. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to
15 that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the stomach. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or
20 disorder of the stomach. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human
25 mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the stomach.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or
30 disorder of the stomach. This method includes the steps of (a) providing a transgenic non-

human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the stomach.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the stomach. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 28 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the stomach.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the stomach. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the stomach.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the stomach. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted

with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the stomach. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

5 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 28 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the stomach.

10 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 28 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the stomach.

15 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 28 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the stomach.

25 In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 28 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the stomach. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the stomach that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include acute erosive gastropathy, acute gastric ulcers, adenocarcinomas, adenomas, adenomatous polyps, advanced gastric cancer, ampullary carcinoma, atrophic gastritis, bacterial gastritis, 5 carcinoid tumors, carcinoma of the stomach, chemical gastritis, chronic (nonerosive) gastritis, chronic idiopathic gastritis, chronic nonatrophic gastritis, Chronkhite-Canada syndrome, congenital cysts, congenital diaphragmatic hernias, congenital diverticula, congenital duplications, congenital pyloric stenosis, congestive gastropathy, cyclic vomiting syndrome, decreased mucosal resistance to acid, diffuse or infiltrating adenocarcinoma, 10 early gastric cancer, emphysematous gastritis, endocrine cell hyperplasia, environmental gastritis, eosinophilic gastritis, eosinophilic gastroenteritis, epithelial polyps, erosive (acute) gastritis, fundic gland polyps, fungal gastritis, gangliocytic paragangliomas, gastral antral vascular ectasia, gastric adenocarcinoma, gastric outlet obstruction (pyloric stenosis), gastric ulcers, gastritis, gastroesophageal reflux, gastroparesis, granulomatous gastritis, H. 15 Pylori infection, hamartomatous polyps, heterotopias, heterotopic pancreatic tissue, heterotopic polyps, hyperplastic gastropathy, hyperplastic polyps, hypersecretion of acid, infectious gastritis, inflammatory lesions of the stomach, inflammatory polyps, intestinal metaplasia, invasive carcinoma, ischemia, leiomyoma, linitis plastica, lumenally acting toxic chemicals, lymphocytic gastritis, lymphomas, malignant gastric stromal neoplasms, 20 malignant lymphoma, malignant transformation of a benign gastric ulcer, Menentrier's disease (hypertrophic gastritis, rugal hypertrophy), mesenchymal neoplasms, metastatic tumors, mucosal polyps, myoepithelial adenomas, myoepithelial hamartomas, neoplasms, neuroendocrine hyperplasias, neuroendocrine tumors, nonerosive gastritis and stomach cancer, nonneoplastic polyps, parasitic gastritis, peptic ulcer disease, phlegmonous gastritis, 25 plasma cell gastritis, polypoid (fungating) adenocarcinoma, poorly differentiated neuroendocrine carcinomas, precancerous lesions, Puetz-Jeghers syndrome, pyloric atresia, rapid gastric emptying, reflux of bile, stress ulcers, stromal tumors, superficial gastritis, type A chronic gastritis (autoimmune gastritis and pernicious anemia), type B chronic gastritis (chronic antral gastritis, H. Pylori gastritis), ulcerating adenocarcinoma, vasculitis, viral 30 gastritis, xanthomatous gastritis, and Zollinger-Ellison syndrome.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 28.

5 In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 28.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 28.

10 In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 28.

In another aspect, the invention features a method of preventing or treating a disease of the testes including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, operably linked to a promoter.

15 In still another aspect, the invention features a method of treating or preventing a disease of the testes including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33.

20 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the testes. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the testes. The GPCR polypeptide can be in a cell or in a cell-free assay system.

25 In yet another aspect, the invention features a method for determining whether a

candidate compound is a compound that may be useful for the treatment of a disease or disorder of the testes. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the testes.

10 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the testes. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33; (b)
15 contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease disease or disorder of the testes.

20 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the testes. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 29 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with
25 the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the testes.

In another aspect, the invention features yet another method for determining whether
30 a candidate compound may be useful for the treatment of a disease or disorder of the testes.

This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate
5 compound may be useful for the treatment of a disease or disorder of the testes.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the testes. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33; (b) contacting the polypeptide with the
10 candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the testes. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

15 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the testes. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 29 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the testes.

20 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the testes. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 29 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the testes.

25 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the testes. The method
30 includes measuring biological activity of a GPCR polypeptide from the patient that is

substantially identical to a polypeptide listed in Tables 29 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the testes.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the testes. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 29 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the testes. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the testes that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include aberrant ducts of Haller, abnormal productions of hormones, abnormalities of testicular descent, acute epididymoorchitis, adenomatoid tumor, adenomatous hyperplasia of the rete testis, adenovirus, administration of estrogens, adrenal rests, alcoholic cirrhosis, amyloidosis, anorchism, appendix testes, bacterial infections, Brucella, cachexia, carcinoma in situ, carcinoma of the rete testis, chlamydia, choriocarcinoma, choristomas, chronic fibrosing epididymoorchitis, coxsackie virus B, cryptorchidism, cystic dysplasia of the rete testis, cytomegalovirus, dystopia, E. coli, Echinococcus granulosus, ectopic testes, embryonal carcinoma, epididymoorchitis, Fournier's scrotal gangrene, fungal infection, germ cell aplasia, germ cell neoplasms, gonadal dysgenesis, gonadal stromal neoplasms, granulomatous orchitis, granulosa cell tumors, Haemophilus influenzae, HIV, hypergonadism, hypogonadotropic hypogonadism, hypopituitarism, hypospermatogenesis, hydrocele, idiopathic granulomatous orchitis, incomplete maturation arrest, infarction, infertility, inflammatory diseases, inflammatory lesions, interstitial (Leydig) cell tumors, Klinefelter's syndrome, latrogenic lesions, Leydig cell tumors, malaknock outplakia, malignant lymphoma, malnutrition, maturation arrest of spermatogenesis, metastatic tumors, mixed germ cell tumors, monorchism, mumps orchitis, mycobacteria, Neisseria gonorrhoeae, neoplasms, obstruction to outflow of semen, orchitis, parasitic infection, polyorchidism, radiation, Salmonella, sarcoidosis, Schistosoma haematobium, seminoma,

Sertoli cell tumors, sex cord stromal tumors, sperm granuloma, spermatocytic seminoma, syphilis, teratocarcinoma, teratoma, testicular atrophy, testicular neoplasms, testicular torsion, Treponema pallidum, tuberculous epididymoorchitis, tumors of nonspecific stroma, undescended testes, uropathogens, varicocele, vascular disturbances, vasculitis, viral
5 infection, Wuchereria bancrofti, and yolk sac carcinoma.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 29.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse),
10 having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 29.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 29.

15 In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 29.

In another aspect, the invention features a method of preventing or treating a disease of the thymus including introducing into a human an expression vector that includes a
20 nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a disease of the thymus including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a
25 polypeptide listed in Tables 30 and 33.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the thymus. This method includes the steps of (a) providing a GPCR
polypeptide substantially identical to a polypeptide listed in Tables 30 and 33; (b)
30 contacting the GPCR polypeptide with the candidate compound; and (c) measuring

biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thymus. The GPCR polypeptide can be in a cell or in a cell-free assay system.

5 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the thymus. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30
10 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thymus.

15 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the thymus. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33; (b)
20 contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease disease or disorder of the thymus.

25 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the thymus. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 30 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with
30 the candidate compound; and (c) measuring reporter activity, wherein altered reporter

activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thymus.

In another aspect, the invention features yet another method for determining whether
5 a candidate compound may be useful for the treatment of a disease or disorder of the thymus. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate
10 compound may be useful for the treatment of a disease or disorder of the thymus.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the thymus. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33; (b) contacting the polypeptide with the
15 candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thymus. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

20 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the thymus. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 30 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the thymus.

25 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the thymus. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 30 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of
30 the thymus.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

5 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the thymus. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 30 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the thymus.

10 In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the thymus. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 30 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the
15 thymus. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the thymus that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include
20 accidental involution, acute accidental involution, acute lymphoblastic leukemia of T cell type, agenesis, age-related involution, anaplastic carcinoma, ataxia telangiectasia, atrophy, bacterial infections, bacterial mediastinitis, basaloid carcinoma, bone marrow transplantation, Bruton's agammaglobulinemia, carcinosarcoma, chronic accidental
25 involution, clear cell carcinoma, cortical thymoma, cytomegalovirus, DiGeorge syndrome, dysgenesis, dysplasia with pattern similar to severe atrophy, dysplasia with pseudoglandular appearance, dysplasia with stromal conticomedullary differentiation, ectopia, germ cell
tumors, Grave's disease, histiocytosis X, HIV, Hodgkin's disease, hyperplasia, infectious mononucleosis, involution, lymphoblastic lymphoma of T-cell type, lymphoepithelioma-like carcinoma, lymphofollicular thymitis, maldescent, malignant lymphomas, malignant
thymoma, measles giant cell pneumonia, medullary thymoma, mixed (composite) thymoma,
30 mucoepidermoid carcinoma, myasthenia gravis, neonatal syphilis, neoplasms, Omenn's

syndrome, predominantly cortical (organoid) thymoma, primary mediastinal B-cell lymphoma of high-grade malignancy, sarcomatoid carcinoma, seminoma, severe combined immunodeficiency, short limb dwarfism, simple dysplasia, small cell carcinoma, small-cell B-cell lymphoma of MALT type, squamous cell carcinoma, systemic lupus erythematosus, 5 teratoma, thymic carcinoid, thymic carcinoma, thymic cysts, thymic epithelial cysts, thymic epithelial tumorw, thymic neoplasms, thymitis with diffuse B-cell infiltrations, thymolipoma, thymoma, true thymic hyperplasia, varicella-zoster, viral infections, well differentiated thymic carcinoma, and Wiscott-Aldrich syndrome.

In another aspect, the invention features a non-human mammal (e.g., a mouse), 10 having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 30.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 30.

15 In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 30.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to 20 a polypeptide listed in Table 30.

In another aspect, the invention features a method of preventing or treating a disease of the thyroid including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, operably linked to a promoter.

25 In still another aspect, the invention features a method of treating or preventing a disease of the thyroid including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33.

In yet another aspect, the invention features a method for determining whether a 30 candidate compound is a compound that may be useful for the treatment of a disease or

disorder of the thyroid. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thyroid. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the thyroid. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of transgenic non-human mammal, wherein altered biological activity, relative to that of the GPCR transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thyroid.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the thyroid. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thyroid.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the thyroid. This method includes (a) providing a nucleic acid molecule comprising a

promoter from a gene encoding a GPCR polypeptide listed in Tables 31 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that
5 the candidate compound may be useful for the treatment of a disease or disorder of the thyroid.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the thyroid. This method includes the steps of: (a) providing a GPCR polypeptide substantially
10 identical to a polypeptide listed in Tables 31 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thyroid.

In still another aspect, the invention features another method for determining
15 whether a candidate compound may be useful for the treatment of a disease or disorder of the thyroid. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted
20 with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the thyroid. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid. The method
25 includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 31 and 33, wherein presence of the mutation indicates that the patient may have an increased risk for developing a disease or disorder of the thyroid.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid. This
30 method includes the step of determining whether the patient has a polymorphism in a gene

encoding a polypeptide listed in Tables 31 and 33, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the thyroid.

5 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

10 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 31 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the patient may have an increased risk for developing a disease or disorder of the thyroid.

15 In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 31 and 33, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the thyroid. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

20 Diseases of the thyroid that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include aberrant thyroid glands, accessory thyroid glands, adenoma with bizarre nuclei, agenesis, amphicrine variant of medullary carcinoma, anaplastic (undifferentiated) carcinoma, aplasia, atrophic thyroiditis, atypical adenoma, autoimmune thyroiditis, carcinoma, C-cell hyperplasia, clear
25 cell tumors, clear cell variant of medullary carcinoma, colloid adenoma, columnar variant of papillary carcinoma, congenital hypothyroidism (cretinism), diffuse nontoxic goiter, diffuse sclerosing variant of papillary carcinoma, dys hormonogenic goiter, embryonal adenoma, encapsulated variant of papillary carcinoma, endemic cretinism, endemic goiter, enzyme deficiency, fetal adenoma, follicular adenoma, follicular carcinoma, follicular variant of
30 medullary carcinoma, follicular variant of papillary carcinoma, fungal infection, giant cell

variant of medullary carcinoma, goiter induced by antithyroid agents, goitrous hypothyroidism, Graves' disease, Hashimoto's autoimmune thyroiditis, Hürthle cell (oncocytic) adenoma, hyalinized trabecular adenoma, hyperthyroidism, hypothyroid cretinism, hypothyroidism, iodine deficiency, juvenile thyroiditis, latrogenic

5 hypothyroidism, lingual thyroid glands, malignant lymphoma, medullary carcinoma, melanocytic variant of medullary carcinoma, mesenchymal tumors, metastatic tumors, minimally invasive follicular carcinoma, mixed medullary and follicular carcinoma, mixed medullary and papillary carcinoma, mucinous carcinoma, mucoepidermoid carcinoma, multinodular goiter, myxedema, neoplasms, neurologic cretinism, nonspecific lymphocytic

10 (simple chronic) thyroiditis, oncocytic variant of medullary carcinoma, palpation thyroiditis, papillary carcinoma, papillary microcarcinoma, papillary variant of medullary carcinoma, partial agenesis, pituitary thyrotropic adenoma, poorly differentiated carcinoma, primary hypothyroidism, pseudopapillary variant of medullary carcinoma, Riedel's thyroiditis, sclerosing mucoepidermoid carcinoma with eosinophilia, silent thyroiditis, simple adenoma,

15 small cell variant of medullary carcinoma, solitary thyroid nodule, sporadic goiter, squamous cell carcinoma, squamous variant of medullary carcinoma, subacute thyroiditis (DeQuervain, granulomatous, giant cell thyroiditis), tall cell variant of papillary carcinoma, tertiary syphilis, thyroglossal duct cyst, thyroid agenesis, thyroid nodules, thyroiditis, thyrotoxicosis, toxic adenoma, toxic multinodular goiter, toxic nodular goiter (Plummer's

20 disease), tuberculosis, tubular variant of medullary carcinoma, and widely invasive follicular carcinoma.

In another aspect, the invention features a non-human mammal (e.g., a mouse), having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 31.

25 In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 31.

In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially

30 identical to a polypeptide listed in Table 31.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 31.

5 In another aspect, the invention features a method of preventing or treating a disease of the uterus including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, operably linked to a promoter.

10 In still another aspect, the invention features a method of treating or preventing a disease of the uterus including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33.

15 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the uterus. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the uterus. The GPCR polypeptide
20 can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the uterus. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule
25 encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33; (b) contacting transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the
30 treatment of a disease or disorder of the uterus.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the uterus. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the uterus.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the uterus. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Tables 32 and 33, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the uterus.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the uterus. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the uterus.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the uterus. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33; (b) contacting the polypeptide with the

candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the uterus. Preferably the GPCR polypeptide is in a cell or a cell
5 free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Tables 32 and 33, wherein presence of the mutation indicates that the
10 patient may have an increased risk for developing a disease or disorder of the uterus.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Tables 32 and 33, wherein presence of the polymorphism indicates
15 that the patient may have an increased risk for developing a disease or disorder of the uterus.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

20 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Tables 32 and 33, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicate that the
25 patient may have an increased risk for developing a disease or disorder of the uterus.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Tables 32 and 33, wherein altered levels in the expression, relative to normal,
30 indicate that the patient has an increased risk for developing a disease or disorder of the

uterus. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the uterus that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include acute

5 cervicitis, acute endometritis, adenocanthoma, adenocarcinoma, adenocarcinoma in situ, adenoid cystic carcinoma, adenomatoid tumor, adenomyoma, adenomyosis (endometriosis interna), adenosquamous carcinoma, amebiasis, arias-Stella phenomenon, atrophy of the endometrium, atypical hyperplasia, benign polypoid lesions, benign stromal nodule, carcinoid tumors, carcinoma in situ, cervical intraepithelial neoplasia, chlamydia, chronic

10 cervicitis, chronic nonspecific endometritis, ciliated (tubal) metaplasia, clear cell adenocarcinoma, clear cell carcinoma, clear cell metaplasia, complex hyperplasia with atypia, complex hyperplasia without atypia, condyloma aduminatum, congenital abnormalities, corpus cancer syndrome, cystic hyperplasia, dysfunctional uterine bleeding, dysmenorrhea, dysplasia of the cervix (cervical intraepithelial neoplasia, squamous

15 intraepithelial lesion), endocervical adenocarcinoma, endocervical polyp, endolymphatic stromal myosis, endometrial adenocarcinoma, endometrial carcinoma, endometrial hyperplasia, endometrial polyps, endometrial stromal neoplasms, endometriosis, endometritis, endometroid (pure) adenocarcinoma of the endometrium, endometroid adenocarcinoma with squamous differentiation, eosinophilic metaplasia, epimenorrhea,

20 exogenous progestational hormone effect, extrauterine endometriosis (endometriosis externa), gestational trophoblastic disease, gonorrhea, hemangioma, herpes simplex virus type 2, high-grade squamous intraepithelial lesion, human papillomavirus, hyperplasia, inadequate luteal phase, infertility, inflammatory cervical lesions, inflammatory lesions of the endometrium, intravenous leiomyomatosis, invasive carcinoma of cervix, invasive

25 squamous cell carcinoma, leiomyoma, leiomyosarcoma, lipoma, low-grade squamous intraepithelial lesion, malignant mixed mesodermal (Müllerian) tumor, menorrhagia, metaplasia, metastasizing leiomyoma, metastatic carcinoma, microglandular hyperplasia, microinvasive carcinoma, microinvasive squamous cell carcinoma, mucinous adenocarcinoma, mucinous metaplasia, neoplasms of the cervix, neoplasms of the

30 endometrium, neoplasms of the myometrium, nonneoplastic cervical proliferations,

papillary syncytial metaplasia, papilloma, pelvic inflammatory disease, peritoneal leiomyomatosis, persistent luteal phase, postmenopausal bleeding, serous papillary adenocarcinoma, simple hyperplasia with atypia, simple hyperplasia without atypia, spontaneous abortion, squamous carcinoma, squamous cell neoplasia, squamous
5 intraepithelial lesions, squamous metaplasia, squamous metaplasia (acanthosis), stromal sarcoma, tuberculous endometritis, unopposed estrogen effect, uterine leiomyomata, verrucous carcinoma, vestigial and heterotopic structures, villoglandular papillary adenocarcinoma, and viral endometritis.

In another aspect, the invention features a non-human mammal (e.g., a mouse),
10 having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 32.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 32.

15 In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 32.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 32.
20

In another aspect, the invention features a method of preventing or treating a disease of the pancreas including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a promoter.

25 In still another aspect, the invention features a method of treating or preventing a disease of the pancreas including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

In yet another aspect, the invention features a method for determining whether a
30 candidate compound is a compound that may be useful for the treatment of a disease or

disorder of the pancreas. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the pancreas. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the pancreas. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the pancreas.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the pancreas. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the pancreas.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the pancreas. This method includes (a) providing a nucleic acid molecule comprising a

promoter from a gene encoding a GPCR polypeptide listed in Table 1, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the pancreas.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the pancreas. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the pancreas.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the pancreas. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the pancreas. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Table 1, wherein presence of the mutation indicates that the patient has an increased risk for developing a disease or disorder of the pancreas.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas. This method includes the step of determining whether the patient has a polymorphism in a gene

encoding a polypeptide listed in Table 1, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the pancreas.

5 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas. The method includes measuring biological activity of a GPCR polypeptide from the patient that
10 is substantially identical to a polypeptide listed in Table 1, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicates that the patient has an increased risk for developing a disease or disorder of the pancreas.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas.
15 The method includes the step of measuring the patient's expression levels of a polypeptide listed in Table 1, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the pancreas. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

20 Diseases of the pancreas that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include ACTHoma, acute pancreatitis, adult onset diabetes, annulare pancreas, carcinoid syndrome, carcinoid tumors, carcinoma of the pancreas, chronic pancreatitis, congenital cysts, Cushing's syndrome, cystadenocarcinoma, cystic fibrosis (mucoviscidosis, fibrocystic
25 disease), diabetes mellitus, ectopic pancreatic tissue, gasterinoma, gastrin excess, glucagon excess, glucagonomas, GRFomas, hereditary pancreatitis, hyperinsulinism, impaired insulin release, infected pancreatic necrosis, insulin resistance, insulinomas, islet cell hyperplasia, islet cell neoplasms, juvenile onset diabetes, macroamylase mia, maldevelopment of the pancreas, maturity-onset diabetes of the young, metastatic neoplasms, mucinous
30 cystadenoma, neoplastic cysts, nonfunctional pancreatic endocrine tumors, pancreas

divisum, pancreatic abcess, pancreatic cancer, pancreatic cholera, pancreatic cysts, pancreatic endocrine tumor causing carcinoid syndrome, pancreatic endocrine tumor causing hypercalcemia, pancreatic endocrine tumors, pancreatic exocrine insufficiency, pancreatic pleural effusion, pancreatic polypeptide excess, pancreatic pseudocyst, pancreatic
5 trauma, pancreatogenous ascites, serous cystadenoma, Shwachman's syndrome, somatostatin excess, somatostatinoma syndrome, traumatic pancreatitis, type 1 (insulin-dependent) diabetes, type 2 (non-insulin-dependent) diabetes, vasoactive intestinal polypeptide excess, VIPomas, Zollinger-Ellison syndrome.

In another aspect, the invention features a non-human mammal (e.g., a mouse),
10 having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

In yet another aspect, the invention features a non-human mammal (e.g., a mouse), having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

15 In a related aspect, the invention features a cell from a non-human mammal having a transgene that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

In another aspect, the invention features a cell from a non-human mammal having a mutation in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to
20 a polypeptide listed in Table 1.

In another aspect, the invention features a method of preventing or treating a disease of the bone and joints including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a promoter.

25 In still another aspect, the invention features a method of treating or preventing a disease of the bone and joints including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

In yet another aspect, the invention features a method for determining whether a
30 candidate compound is a compound that may be useful for the treatment of a disease or

disorder of the bone and joints. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the bone and joints. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the bone and joints. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the bone and joints.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the bone and joints. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the bone and joints.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the bone and joints. This method includes (a) providing a nucleic acid molecule comprising

a promoter from a gene encoding a GPCR polypeptide listed in Table 1, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the bone and joints.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the bone and joints. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the bone and joints.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the bone and joints. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the bone and joints. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the bone and joints. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Table 1, wherein presence of the mutation indicates that the patient has an increased risk for developing a disease or disorder of the bone and joints.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the bone and joints. This method includes the step of determining whether the patient has a polymorphism in a

gene encoding a polypeptide listed in Table 1, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the bone and joints.

In either of these two methods, the mutation or polymorphism is preferably
5 associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the bone and joints. The method includes measuring biological activity of a GPCR polypeptide from the patient
10 that is substantially identical to a polypeptide listed in Table 1, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicates that the patient has an increased risk for developing a disease or disorder of the bone and joints.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the bone and
15 joints. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Table 1, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the bone and joints. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

20 Diseases of the bone and joints that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include achondroplasia, acute bacterial arthritis, acute pyogenic osteomyelitis, Albright's syndrome, alkaptonuria (ochronosis), aneurysmal bone cyst, ankylosing spondylitis, arthritic, arthropathies associated with hemoglobinopathies, arthropathy of acromegaly, arthropathy
25 of hemochromatosis, bone cysts, calcium hydroxyapatite deposition disease, calcium pyrophosphate deposition disease, chondrocalcinosis, chondroma, chondrosarcoma, chondrochondritis, chondromblastoma, congenital dislocation of the hip, congenital disorders of joints, echondromatosis (dyschondroplasia, Ollier's disease), erosive osteoarthritis, Ewing's sarcoma, Felty's syndrome, fibromyalgia, fibrous cortical defect,
30 fibrous dysplasia (McCune-Albright syndrome, fungal arthritis, ganglion, giant cell tumor,

gout, hematogenous osteomyelitis, hemophilic arthropathy, hereditary hyperphosphatasia, hyperostosis, hyperostosis frontalis interna, hyperparathyroidism (osteitis fibrosa cystica), hypertrophic osteoarthropathy, infections diseases of joints, juvenile rheumatoid arthritis (Still's disease), lyme disease, lymphoid neoplasms, melorheostosis, metabolic diseases of joints, metastatic carcinoma, metastatic neoplasms, monostatic fibrous dysplasia, multiple exostoses (diaphyseal aclasis, osteochondromatosis), neoplasms, neuropathic joint (Charcot's joint), osteoarthritis, osteoarthrosis, osteoblastoma, osteochondroma (exostosis), osteogenesis imperfecta (brittle bone disease), osteoid osteoma, osteoma, osteomalacia, osteomyelitis, osteomyelosclerosis, osteopetrosis (marbel bone disease, Albers-Schönberg disease), osteopoikilosis, osteoporosis (osteopenia), osteosarcoma, osteosclerosis, Paget's disease of bone (osteitis deformans), parasitic arthritis, parosteal osteosarcome, pigmented villonodular synovitis, polyostotic fibrous dysplasia, postinfectious or reactive arthritis, progressive diaphyseal dysplasia (Camurati-Engelmann disease), pseudogout, psoriatic arthritis, pyknodysostosis, pyogenic arthritis, reflex sympathetic dystrophy syndrome, relapsing polychondritis, rheumatoid arthritis, rickets, senile osteoporosis, sickle cell disease, spondyloepiphyseal dysplasia, synovial chondromatosis, synovial sarcoma, syphilitic arthritis, talipes calcaneovalgus, talipes equinovarus, thalassemia, Tietze's syndrome, tuberculosis of bone, tuberculous arthritis, unicameral bone cyst (solitary bone cyst), viral arthritis.

20 In another aspect, the invention features a method of preventing or treating a disease of the breast including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a promoter.

25 In still another aspect, the invention features a method of treating or preventing a disease of the breast including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

30 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the breast. This method includes the steps of (a) providing a GPCR polypeptide

substantially identical to a polypeptide listed in Table 1; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the breast. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the breast. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the breast.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the breast. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the breast:

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the breast. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Table 1, the promoter

operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the breast.

5 In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the breast. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide.

10 Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the breast.

 In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the breast. This method includes (a) providing a GPCR polypeptide substantially identical
15 to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the breast. Preferably the GPCR polypeptide is in a cell or a cell free
20 assay system.

 In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the breast. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Table 1, wherein presence of the mutation indicates that the patient has
25 an increased risk for developing a disease or disorder of the breast.

 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the breast. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Table 1, wherein presence of the polymorphism indicates that the
30 patient may have an increased risk for developing a disease or disorder of the breast.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

5 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the breast. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Table 1, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicates that the patient has an increased risk for developing a disease or disorder of the breast.

10 In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the breast. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Table 1, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the breast.

15 Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Diseases of the breast that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include acute mastitis, breast abscess, carcinoma, chronic mastitis, congenital breast anomalies, cystic mastopathy, ductal carcinoma, ductal carcinoma in situ, ductal papilloma, fat necrosis, fibroadenoma, fibrocystic changes, fibrocystic disease, galactorrhea, granular cell tumor, gynecomastia, infiltrating ductal carcinoma, inflammatory breast carcinoma, inflammatory breast lesions, invasive lobular carcinoma, juvenile hypertrophy of the breast, lactating adenoma, lobular carcinoma in situ, neoplasms, Paget's disease of the nipple, phyllodes tumor (cystosarcome phyllodes), polymastia, polymazia, polythelia, silicone granuloma, supernumerary breast, and supernumerary nipples.

25 In another aspect, the invention features a method of preventing or treating a disease of the immune system including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a promoter.

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In still another aspect, the invention features a method of treating or preventing a disease of the immune system including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

5 In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a disease or disorder of the immune system. This method includes the steps of (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of
10 the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the immune system. The GPCR polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a
15 candidate compound is a compound that may be useful for the treatment of a disease or disorder of the immune system. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the transgenic non-human mammal with the candidate compound;
20 and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the immune system.

In yet another aspect, the invention features a method for determining whether a
25 candidate compound is a compound that may be useful for the treatment of a disease or disorder of the immune system. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Table 1; (b) contacting the transgenic non-human mammal with the candidate compound;
30 and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human

mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the immune system.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the immune system. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Table 1, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the immune system.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the immune system. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a disease or disorder of the immune system.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a disease or disorder of the immune system. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a disease or disorder of the immune system. Preferably the GPCR polypeptide is in a cell or a cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system. The

method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Table 1, wherein presence of the mutation indicates that the patient has an increased risk for developing a disease or disorder of the immune system.

5 In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Table 1, wherein presence of the polymorphism indicates that the patient may have an increased risk for developing a disease or disorder of the immune system.

10 In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system.

15 The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Table 1, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicates that the patient has an increased risk for developing a disease or disorder of the immune system.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Table 1, wherein altered levels in the expression, relative to normal, indicate that the patient has an increased risk for developing a disease or disorder of the immune system. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

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Diseases of the immune system that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include abnormal neutrophil function, acquired immunodeficiency, acute rejection, Addison's disease, advanced cancer, aging, allergic rhinitis, angioedema, arthrus-type hypersensitivity reaction, ataxia-telangiectasia, autoimmune disorders, autoimmune gastritis, autosomal

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recessive agammaglobulinemia, blood transfusion reactions, Bloom's syndrome, Bruton's
 congenital agammaglobulinemia, bullous pemphigoid, Chédiak-Higashi syndrome, chronic
 active hepatitis, chronic granulomatous disease of childhood, chronic rejection, chronic
 renal failure, common variable immunodeficiency, complement deficiency, congenital
 5 (primary) immunodeficiency, contact dermatitis, deficiencies of immune response,
 deficiency of the vascular response, dermatomyositis, diabetes mellitus, disorders of
 microbial killing, disorders of phagocytosis, Goodpasture's syndrome, graft rejection, graft-
 versus-host disease, granulocyt deficiency, granulocytic leukemia, Graves' disease,
 Hashimoto's thyroiditis, hemolytic anemia, hemolytic disease of the newborn, HIV
 10 infection (AIDS), Hodgkin's disease, hyperacute rejection, hyper-IgE syndrome,
 hypersensitivity pneumonitis, hypoparathyroidism, IgA deficiency, IgG subclass
 deficiencies, immunodeficiency with thymoma, immunoglobulin deficiency syndromes,
 immunologic hypersensitivity, immunosuppressive drug therapy, infertility, insulin-resistant
 diabetes mellitus, interferon γ receptor deficiency, interleukin 12 receptor deficiency, iron
 15 deficiency, juvenile insulin-dependent diabetes mellitus, Kaposi's sarcoma, lazy leuknock
 outcyte syndrom, localized type 1 hypersensitivity, lymphocytic leukemia, lymphoma,
 malignant B cell lymphoma, major histocompatibility complex class 2 deficiency, mixed
 connective tissue disease, multiple myeloma, myasthenia gravis, myeloperoxidase
 deficiency, neutropenia, nude syndrome, pemphigus vulgaris, pernicious anemia,
 20 postinfectious immunodeficiency, primary biliary cirrhosis, primary immunodeficiency,
 primary T cell immunodeficiency, progressive systemic sclerosis, protein-calorie
 malnutrition, purine nucleoside phosphorylation deficiency, rheumatic fever, rheumatoid
 arthritis, secondary immunodeficiency, selective (isolated) IgA deficiency, serum sickness
 type hypersensitivity reaction, severe combined immunodeficiency, Sjögren's syndrome,
 25 sympathetic ophthalmitis, systemic lupus erythematosus, systemic mastocytosis, systemic
 type 1 hypersensitivity, T cell receptro deficiency, T lymphopenia (Nezelof's syndrome),
 thrombocytopenia, thymic hypoplasia (DiGeorge syndrome), thymic neoplasms, thymoma
 (Goode's syndrome), transient hypogammaglobulinemia of infancy, type 1 (immediate)
 hypersensitivity (atopy, anaphylaxis), type 2 hypersensitivity, type 3 hypersensitivity
 30 (immune complex injury), type 4 (delayed) hypersensitivity, urticaria, variable

immunodeficiency, vitiligo, Wisknack outtt-Aldrich syndrom, x-linked agammaglobulinemia, x-linked immunodeficiency with hyper IgM, x-linked lymphoproliferative syndrome, zap70 tyrosine kinase deficiency.

In another aspect, the invention features a method of preventing or treating a
5 metabolic or nutritive disease or disorder, including introducing into a human an expression vector that includes a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a promoter.

In still another aspect, the invention features a method of treating or preventing a
10 metabolic or nutritive disease or disorder, including administering to an animal (e.g., a human) a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder. This method includes the steps of (a) providing a GPCR
15 polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the GPCR polypeptide with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide, wherein altered biological activity, relative to that of the GPCR polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder. The GPCR
20 polypeptide can be in a cell or in a cell-free assay system.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a knock-out mouse) having a disruption in a nucleic acid
25 molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be
30 useful for the treatment of a metabolic or nutritive disease or disorder.

In yet another aspect, the invention features a method for determining whether a candidate compound is a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder. This method includes the steps of (a) providing a transgenic non-human mammal (e.g., a mouse) overexpressing a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Table 1; (b) contacting the transgenic non-human mammal with the candidate compound; and (c) measuring biological activity of the GPCR polypeptide in the transgenic non-human mammal, wherein altered biological activity, relative to that of the transgenic non-human mammal not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder. This method includes (a) providing a nucleic acid molecule comprising a promoter from a gene encoding a GPCR polypeptide listed in Table 1, the promoter operably linked to a reporter system; (b) contacting the nucleic acid molecule with the candidate compound; and (c) measuring reporter activity, wherein altered reporter activity, relative to a nucleic acid molecule not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder.

In another aspect, the invention features yet another method for determining whether a candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder. This method includes the steps of: (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate compound; and (c) measuring interaction of the candidate compound to the polypeptide. Interaction of the compound to the polypeptide indicates that the candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder.

In still another aspect, the invention features another method for determining whether a candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder. This method includes (a) providing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1; (b) contacting the polypeptide with the candidate

compound; and (c) measuring the half-life of the polypeptide, wherein an alteration in the half-life of the polypeptide, relative to that of the polypeptide not contacted with the compound, indicates that the candidate compound may be useful for the treatment of a metabolic or nutritive disease or disorder. Preferably the GPCR polypeptide is in a cell or a
5 cell free assay system.

In another aspect, the invention features a method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder. The method includes the step of determining whether the patient has a mutation in a gene encoding a polypeptide listed in Table 1, wherein presence of the mutation indicates that the
10 patient has an increased risk for developing a metabolic or nutritive disease or disorder.

In a related aspect, the invention features another method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder. This method includes the step of determining whether the patient has a polymorphism in a gene encoding a polypeptide listed in Table 1, wherein presence of the polymorphism
15 indicates that the patient may have an increased risk for developing a metabolic or nutritive disease or disorder.

In either of these two methods, the mutation or polymorphism is preferably associated with an alteration (for example, a decrease) in the biological activity of the polypeptide.

20 In another aspect, the invention features another method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder. The method includes measuring biological activity of a GPCR polypeptide from the patient that is substantially identical to a polypeptide listed in Table 1, wherein increased or decreased levels in the GPCR biological activity, relative to normal levels, indicates that the
25 patient has an increased risk for developing a metabolic or nutritive disease or disorder.

In still another aspect, the invention features yet another method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder. The method includes the step of measuring the patient's expression levels of a polypeptide listed in Table 1, wherein altered levels in the expression, relative to normal,
30 indicate that the patient has an increased risk for developing a metabolic or nutritive disease

or disorder. Preferably, the expression levels are determined by measuring levels of polypeptide or mRNA.

Preferred metabolic or nutritive diseases and disorders that can be treated or diagnosed using the methods of the invention or for which candidate therapeutic compounds may be identified include 5,10-methylenetetrahydrofolate reductase deficiency, achondrogenesis type 1B, acid α -1,4 glucosidase deficiency, acquired generalized lipodystrophy (Lawrence syndrome), acquired partial lipodystrophy (Barraquer-Simons syndrome), acute intermittent porphyria, acute panniculitis, adenine phosphoribosyltransferase deficiency, adenosine deaminase deficiency, adenylosuccinate lyase deficiency, adiposis dolorosa (Dercum disease), ALA dehydratase-deficient porphyria, albinism, alkaptonuria, amulopectinosis, Andersen disease, argininemia, argininosuccinic aciduria, astelosteogenesis type 2, Bartter's syndrome, benign familial neonatal epilepsy, benign fructosuria, benign recurrent and progressive familial intrahepatic cholestasis, biotin deficiency, branching enzyme deficiency, calcium deficiency, carnitine transport defect, choline deficiency, choline toxicity, chromium deficiency, chronic fat malabsorption, citrullinemia, classic branched-chain ketoaciduria, classic cystinuria, congenital chloridorrhea, congenital erythropoietic porphyria, congenital generalized lipodystrophy, congenital myotonia, copper deficiency, copper toxicity, cystathionine β -synthase deficiency, cystathioninuria, cystic fibrosis, cystinosis, cystinuria, Darier disease, defect in transport of long-chain fatty acids, deficiency of cobalamin coenzyme deficiency, Dent's syndrome, diatrophic dysplasia, dibasic aminoaciduria, dicarboxylic aminoaciduria, dihydropyrimidine dehydrogenase deficiency, distal renal tubular acidosis, dry beriberi, Dubin-Johnson syndrome, dysbetalipoproteinemia, end-organ insensitivity to vitamin D, erythropoietic protoporphyria, Fabry disease, failure of intestinal absorption, familial apoprotein C2 deficiency, familial combined hyperlipidemia, familial defective Apo B100, familial goiter, familial hypercholesterolemia, familial hypertriglyceridemia, familial hypophosphatemic rickets, familial lipoprotein lipase deficiency, familial partial lipodystrophy, Fanconi-Bickel syndrome, fluoride deficiency, folate malabsorption, folic acid deficiency, formiminoglutamic aciduria, fructose 1,6 diphosphatase deficiency, galactokinase deficiency, galactose 1-phosphate uridyl transferase deficiency galactosemia,

Gaucher disease, Gitelman's syndrome, globoid cell leukodystrophy, glucose-6-phosphatase deficiency, glucose-6-translocase deficiency, glucose-galactose malabsorption, glucose-transporter protein syndrome, glutaric aciduria, glycogen storage disease type 2, glycogen storage disease type Ib, glycogen storage disease type ID, glycogen synthase deficiency, gout, Hartnup disease, hawkinsinuria, hemochromatosis, hepatic glycogenosis with renal fanconi syndrome, hepatic lipase deficiency, hepatic porphyria, hereditary coproporphyria, hereditary fructose intolerance, hereditary xanthinuria, Hers disease, histidinemia, histidinuria, HIV-1 protease inhibitor-induced lipodystrophy, homocitrullinuria, homocystinuria, homocystinuria and methylmalonic acidemia, homocystinurias, Hunter syndrome, Hurler disease, Hurler-Scheie disease, hypophosphatemic rickets, hyperammonemia, hyperammonemia, hypercholesterolemia, hypercystinuria, hyperglycinemia, hyperhydroxyprolinemia, hyperkalemic periodic paralysis, hyperleucineisoleucinemia, hyperlipoproteinemias, hyperlysinemia, hypermagnesemia, hypermetabolism, hypermethioninemia, hyperornithinemia, hyperoxaluria, hyperphenylalaninemia with primapterinuria, hyperphenylalaninemias, hyperphosphatemia, hyperprolinemia, hypertriglyceridemia, hyperuricemia, hypervitaminosis A, hypervitaminosis D, hypocholesterolemia, hypometabolism, hypophosphatemia, hypouricemia, hypovitaminosis A, hypoxanthine phosphoribosyltransferase deficiency, iminoglycinuria, iminopeptiduria, intermittent branched-chain ketoaciduria, intestinal malabsorption, iodine deficiency, iron deficiency, isovaleric acidemia, Jervell and Lange-Nielsen syndrome, juvenile pernicious anemia, keshan disease, Knock out/sack knock out's syndrome, kwashiorkor, leukodystrophies, Liddle's syndrome, lipodystrophies, lipomatosis, liver glycogenoses, liver phosphorylase kinase deficiency, long QT syndrome, lysinuria, lysosomal storage diseases, magnesium deficiency, malabsorptive diseases, malignant hyperphenylalaninemia, manganese deficiency, marasmus, Maroteaux-Lamy disease, McArdle disease, Menkes' disease, metachromatic leukodystrophy, methionine malabsorption, methylmalonic acidemia, molybdenum deficiency, monosodiumurate gout, Morquio syndrome, mucopolysaccharidoses, mucopolysaccharidoses, multiple carboxylase deficiency syndrome, multiple symmetric lipomatosis (Madelung disease, muscle glycogenoses, muscle

phosphofructokinase deficiency, muscle phosphorylase deficiency, myoadenylate deaminase deficiency, nephrogenic diabetes insipidus, nesidioblastosis of pancreas, niacin deficiency, niacin toxicity, Niemann-Pick disease, obesity, orotic aciduria, osteomalacia, paramyotonia congenita, pellagra, Pendred syndrome, phenylketonuria, phenylketonuria type 1, phenylketonuria type 2, phenylketonuria type 3, phosphate deficiency, phosphoribosylpyrophosphate synthetase overactivity, polygenic hypercholesterolemia, Pompe disease, porphyria cutanea tarda, porphyrias, primary bile acid malabsorption, primary hyperoxaluria, primary hypoalphalipoproteinemia, propionic acidemia, protein-energy malnutrition, proximal renal tubular acidosis, purine nucleoside phosphorylase deficiency, pyridoxine deficiency, pyrimidine 5'-nucleotidase deficiency, renal glycosuria, riboflavin deficiency, rickets, Rogers' syndrome, saccharopinuria, Sandhoff disease, Sanfilippo syndromes, sarcosinemia, Scheie disease, scurvy (vitamin C deficiency), selenium deficiency, selenosis, sialic acid storage disease, S-sulfo-L-cysteine, sulfite, thiosulfaturia, Tarui disease, Tay-Sachs disease, thiamine deficiency, tryptophan malabsorption, tryptophanuria, type 1 pseudohypoaldosteronism, type 3 glycogen storage disease (debrancher deficiency, limit dextrinosis), tyrosinemia, tyrosinemia type 1, tyrosinemia type 2, tyrosinemia type 3, uridine diphosphate galactose 4-epimerase deficiency, urocanic aciduria, variegate porphyria, vitamin B12 deficiency, vitamin C toxicity, vitamin D deficiency, vitamin D-resistant rickets, vitamin d-sensitive rickets, vitamin E deficiency, vitamin E toxicity, vitamin K deficiency, vitamin K toxicity, von Gierke disease, Wernicke's encephalopathy, wet beriberi, Wilson's disease, xanthurenic aciduria, X-linked sideroblastic anemia, zinc deficiency, zinc toxicity, α -ketoadipic aciduria, α -methylacetoacetic aciduria, β -hydroxy- β -methylglutaric aciduria, β -methylcrotonyl glycinuria.

In another aspect, the invention features a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1. The transgene may be operably linked, e.g., to an inducible, cell-type, or tissue-specific promoter. In one embodiment, the transgenic mouse has a mutation in a gene that is orthologous to the transgene. For example, the transgene encoding the human GPCR polypeptide may entirely replace the coding sequence of the orthologous mouse gene or the transgene might complement a knock

out of the orthologous mouse gene.

In a related embodiment, the transgenic mouse has a mutation (e.g., a deletion, frameshift, insertion or a point mutation) in a gene listed in Table 1.

In another aspect, the invention features an isolated cell or population of cells
5 derived from a transgenic mouse either expressing a transgene encoding a human GPCR polypeptide listed in Table 1 or has a mutation (e.g., a deletion, frameshift, insertion or a point mutation) in a gene listed in Table 1.

The invention also features a method for identifying a compound that may be useful for the treatment of a disease or disorder described herein. The method includes the steps of
10 administering a candidate compound to a transgenic mouse expressing a transgene encoding a GPCR polypeptide listed in Table 1; and determining whether the candidate compound decreases the biological activity of the GPCR polypeptide, wherein a decrease in the biological activity of the GPCR polypeptide identifies the candidate compound as a compound that may be useful for the treatment of a disease or disorder. In one
15 embodiment, the transgenic mouse has a mutation (e.g., a deletion, frameshift, insertion or a point mutation) in a gene listed in Table 1. In a related embodiment, the mouse has a mutation in the gene that is orthologous to the transgene.

In a related aspect, the invention features another method for identifying a compound that may be useful for the treatment of a disease or disorder described herein.
20 This method includes the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a GPCR polypeptide in a gene listed in Table 1, and having a disease or disorder caused by the expression of the transgene; and determining whether the candidate compound treats the disease or disorder.

In a related aspect, the invention features another method for identifying a
25 compound that may be useful for the treatment of a disease or disorder described herein. This method includes the steps of administering a candidate compound to a transgenic mouse transgenic mouse containing a mutation (e.g., a deletion, frameshift, insertion or a point mutation) in a gene listed in Table 1, and having a disease or disorder caused by gene disruption; and determining whether candidate compound treats the disease or disorder.

30 In still another aspect, the invention features a method for identifying a compound

that may be useful for the treatment of a disease or disorder described herein. This method includes the steps of contacting a candidate compound with a cell from a transgenic mouse expressing a transgene encoding a GPCR polypeptide in a gene listed in Table 1; and determining whether the candidate compound decreases the biological activity of the GPCR polypeptide. A decrease in the biological activity of the GPCR polypeptide identifies the candidate compound as a compound that may be useful for the treatment of a disease or disorder. In one embodiment, the transgenic mouse from which the cell was derived has a mutation (e.g., a deletion, frameshift, insertion or a point mutation) in a gene listed in Table 1. In a related embodiment, the mouse has a mutation in the polypeptide that is orthologous to the GPCR polypeptide encoded by the transgene.

The invention also features a kit that includes a plurality of polynucleotides, wherein each polynucleotide hybridizes under high stringency conditions to a GPCR polynucleotide of Table 1. At least 50 different polynucleotides, each capable of hybridizing under high stringency conditions to a different human GPCR polynucleotide listed on Table 1, are present in the kit.

The invention features another kit that includes a plurality of polynucleotides. In this kit, polynucleotides that hybridize under high stringency conditions, each to a different GPCR polynucleotide listed on one of Tables 3-33, are present in the kit such that the kit includes polynucleotides that collectively hybridize to every GPCR polynucleotide listed on one of Tables 3-33.

The invention features another kit, this kit including a plurality of mice, each mouse having a mutation in a GPCR polynucleotide of Table 1, wherein at least 50 mice, each having a mutation in a different GPCR polynucleotide listed on Table 1, are present in the kit. This kit may optionally include a plurality of polynucleotides, wherein each polynucleotide hybridizes under high stringency conditions to a GPCR polynucleotide of Table 1, wherein at least 50 different polynucleotides, each capable of hybridizing under high stringency conditions to a different mouse GPCR polynucleotide listed on Table 1, are present in the kit.

The invention features another kit that includes a plurality of mice having a mutation in a GPCR polynucleotide. In this kit, mice having a mutation in each GPCR

polynucleotide listed on one of Tables 3-33 are present in the kit.

In any of the foregoing kits, at least one of the GPCR polynucleotides is desirably a GPCR polynucleotide of Table 2.

5 Definitions

By "polypeptide" is meant any chain of more than two amino acids, regardless of post-translational modification such as glycosylation or phosphorylation.

By "substantially identical" is meant a polypeptide or nucleic acid exhibiting at least 50%, preferably 85%, more preferably 90%, and most preferably 95% identity to a
10 reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences will generally be at least 16 amino acids, preferably at least 20 amino acids, more preferably at least 25 amino acids, and most preferably 35 amino acids or the full-length polypeptide. For nucleic acids, the length of comparison sequences will generally be at least 50 nucleotides, preferably at least 60 nucleotides, more preferably at least 75
15 nucleotides, and most preferably 110 nucleotides or the full-length polynucleotide.

Sequence identity is typically measured using a sequence analysis program (e.g., BLAST 2; Tatusova et al., FEMS Microbiol Lett. 174:247-250, 1999) with the default parameters specified therein.

By "high stringency conditions" is meant hybridization in 2X SSC at 40°C with a
20 DNA probe length of at least 40 nucleotides. For other definitions of high stringency conditions, see F. Ausubel et al., *Current Protocols in Molecular Biology*, pp. 6.3.1-6.3.6, John Wiley & Sons, New York, NY, 1994, hereby incorporated by reference.

"Substantially identical" polynucleotides also include those that hybridize under high stringency conditions. "Substantially identical" polypeptides include those encoded by
25 polynucleotides that hybridize under high stringency conditions.

By "substantially pure polypeptide" is meant a polypeptide that has been separated from the components that naturally accompany it. Typically, the polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the
30 polypeptide is a GPCR polypeptide that is at least 75%, more preferably at least 90%, and

most preferably at least 99%, by weight, pure. A substantially pure GPCR polypeptide may be obtained, for example, by extraction from a natural source (e.g., a pancreatic cell), by expression of a recombinant nucleic acid encoding a GPCR polypeptide, or by chemically synthesizing the polypeptide. Purity can be measured by any appropriate method, e.g., by
5 column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A polypeptide is substantially free of naturally associated components when it is separated from those contaminants that accompany it in its natural state. Thus, a polypeptide which is chemically synthesized or produced in a cellular system different from the cell from which it naturally originates will be substantially free from its naturally
10 associated components. Accordingly, substantially pure polypeptides include those that naturally occur in eukaryotic organisms but are synthesized in *E. coli*, yeast or other microbial system.

By "purified antibody" is meant antibody that is at least 60%, by weight, free from proteins and naturally occurring organic molecules with which it is naturally associated.
15 Preferably, the preparation is at least 75%, more preferably 90%, and most preferably at least 99%, by weight, antibody. A purified antibody may be obtained, for example, by affinity chromatography using recombinantly-produced protein or conserved motif peptides and standard techniques.

By "specifically binds" is meant any small molecule, peptide, antibody, or
20 polypeptide that recognizes and binds, for example, a human GPCR polypeptide but does not substantially recognize and bind other molecules in a sample, e.g., a biological sample, that naturally includes the protein.

By "polymorphism" is meant that a nucleotide or nucleotide region is characterized as occurring in several different sequence forms. A "mutation" is a form of a
25 polymorphism in which the expression level, stability, function, or biological activity of the encoded protein is substantially altered.

By "GPCR related polypeptide" is meant a polypeptide having substantial identity to any of the polypeptides listed in Table 1, including polymorphic forms (e.g., sequences having one or more SNPs) and splice variants.

30 By "GPCR biological activity" is meant measurable effect or change in an organism

or a cell resulting from the modulation of a GPCR at the molecular, cellular, physiological or behavioral levels or alteration in the extent of activation or deactivation that can be elicited by an agonist or antagonist.

“Dominant negative” means an effect of a mutant form of a gene product that
5 dominately interferes with the function of the normal gene product.

“Reporter system” means any gene, compound or polypeptide whose product can be assayed, measured or monitored. Examples include, but are not limited to neomycin (Kang et al., Mol. Cells; 7:502-508, 1997), luciferase (Welsh et al., Curr. Opin. Biotechnol. 8:617-622, 1997), lacZ (Spergel et al., Prog. Neurobiol. 63:673-686, 2001), aequorin (Deo et al., J.
10 Anal. Chem. 369:258-266, 2001) and green fluorescent protein (Tsien, Annu. Rev. Biochem. 67:509-544, 1998).

“Conditional mutant” is any gene, cell or organism for which the expression of the mutant phenotype can be controlled through alteration in the temperature, diet or other external conditions.

15 “Overexpression” means level of expression higher than the physiological level of expression.

“Isolated” or “purified” means altered from its natural state, i.e., if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living organism is not
20 “isolated,” but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is “isolated,” as the term is employed herein. Moreover, a polynucleotide or polypeptide that is introduced into an organism by transformation, genetic manipulation, or by any other recombinant method is “isolated” even if it is still present in the organism.

25 “Polynucleotide” generally refers to any polyribonucleotide (RNA) or polydeoxribonucleotide (DNA), which may be unmodified or modified RNA or DNA. Polynucleotides include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising
30 DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture

of single- and double-stranded regions. Polynucleotide can also refer to triple helix nucleic acids.

“Variant” refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide, but retains the essential properties thereof. A typical variant of a polynucleotide differs in nucleotide sequence from the reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from the reference polypeptide. Generally, alterations are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, insertions, or deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. Typical conservative substitutions include Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe and Tyr. A variant of a polynucleotide or polypeptide may be naturally occurring such as an allele, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis. Also included as variants are polypeptides having one or more post-translational modifications, for instance glycosylation, phosphorylation, methylation, ADP ribosylation and the like. Embodiments include methylation of the N-terminal amino acid, phosphorylations of serines and threonines and modification of C-terminal glycines.

“Allele” refers to one of two or more alternative forms of a gene occurring at a given locus in the genome.

A “transgenic organism,” as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic

manipulation, such as by microinjection, transfection or by infection with a recombinant virus. The transgenic organisms contemplated in accordance with the present invention include mice, bacteria, cyanobacteria, fungi, plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example
5 infection, transfection, transformation or transconjugation.

A "transgenic mice," as used herein, is a mouse, in which one or more of the cells of the organism contains nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate
10 genetic manipulation, by methods known in the art, for example microinjection, infection, transfection, or transformation.

"Transgene" is any exogenously added nucleic acid.

"Antisense" or "Reverse complement" means a nucleic acid sequence complementary to the messenger RNA.

15 "Single nucleotide polymorphism" or "SNP" refers to the occurrence of nucleotide variability at a single nucleotide position in the genome, within a population. An SNP may occur within a gene or within intergenic regions of the genome. SNPs can be assayed using Allele Specific Amplification (ASA). For this process, at least three primers are required. A common primer is used in reverse complement to the polymorphism being assayed. This
20 common primer can be between 50 and 1500 bps from the polymorphic base. The other two (or more) primers are identical to each other except that the final 3' base wobbles to match one of the two (or more) alleles that make up the polymorphism. Two (or more) PCR reactions are then conducted on sample DNA, each using the common primer and one of the Allele Specific Primers.

25 "Splice variant" as used herein refers to cDNA molecules produced from RNA molecules initially transcribed from the same genomic DNA sequence but which have undergone alternative RNA splicing. Alternative RNA splicing occurs when a primary RNA transcript undergoes splicing, generally for the removal of introns, which results in the production of more than one distinct mRNA molecules each of which may encode different
30 amino acid sequences. The term splice variant also refers to the polypeptides encoded by

the above mRNA molecules.

“Fusion protein” refers to a polypeptide encoded by two, often unrelated, fused genes or fragments thereof.

By “candidate compound” or “test compound” is meant a chemical, be it naturally-
5 occurring or artificially-derived, that is assayed for its ability to modulate gene activity or protein stability or binding, expression levels, or activity, by employing any standard assay method. Test compounds may include, for example, peptides, polypeptides, synthesized organic molecules, naturally occurring organic molecules, polynucleotide molecules, and components thereof.

10 By “promoter” is meant a minimal sequence sufficient to direct transcription. Also included in the invention are those promoter elements which are sufficient to render promoter-dependent gene expression controllable for cell type-specific, tissue-specific, temporal-specific, or inducible by external signals or agents; such elements may be located in the 5’ or 3’ or intron sequence regions of the native gene.

15 By “operably linked” is meant that a gene and one or more regulatory sequences are connected in such a way as to permit gene expression.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof and from the claims.

20 **Brief Description of the Drawings**

FIGURE 1 is a list of GPCR polynucleotides of the invention in human and mouse. Polynucleotides are divided into four classes, A, B, C, and F/S, according to conventional classification of the GPCR superfamily. The “No Class” group includes five
25 polynucleotides that cannot be assigned to any of the above four classes. Within each class, polynucleotides are further grouped into small families based on ligand specificity or, in the case of orphan receptors, significant sequence homology ($\geq 40\%$) within each family. Orphan receptors that cannot be grouped by this criterion are alphabetically listed at the end of each class. Whenever available, names are adopted from the official gene names of the
30 NCBI LocusLink database. Orphan GPCRs are indicated with an asterisk. Abbreviations:

H, human; *M*, mouse; *FMLP*, fMet-Leu-Phe; *GNRH*, gonadotropin-releasing hormone; *PAF*, platelet-activating factor; *INSL3*, insulin-like 3; *SPC*, sphingosylphosphorylcholine; *LPC*, lysophosphatidylcholine; *TRH*, thyrotropin-releasing hormone; *LGR*, leucine-rich repeat-containing G protein-coupled receptor; *SREB*, super conserved receptor expressed in brain; *GIP*, gastric inhibitory polypeptide; *GHRH*, growth hormone-releasing hormone; *PACAP*, pituitary adenylate cyclase activating polypeptide; *DAF*, decay accelerating factor; *GPRC5*, G protein-coupled receptor family C group 5.

FIGURE 2 is a series of phylogenetic trees of human GPCRs. Lines corresponding to individual polynucleotides are colored black for those with known ligands, red for orphan genes, and blue for genes with 7 trans-membrane domains but no homology to known GPCRs. The Class A tree was split into two parts due to size considerations (arrow line indicates the connection). Families are defined as described in Fig. 1. Clusters of GPCRs with significant predictive value as to ligands are highlighted in purple on these bootstrap consensus trees (bootstrap values not shown). The ruler at the bottom of each tree indicates the horizontal distance equal to 10% sequence divergence.

FIGURE 3 is a photograph showing the expression profiles of nine GPCRs as identified by RT-PCR.

FIGURE 4 is schematic summary of tissue expression in 100 GPCR polynucleotides. Polynucleotides were analyzed individually by RT-PCR, as shown in Fig. 3, and the intensity of the observed bands determined by scanning. Each gene is represented by a single row of colored boxes, with four different expression levels: no expression - blue; low expression - purple; moderate expression - dark red; strong expression - pure red. Polynucleotides and tissues, as well as groups of expression patterns, are indicated.

FIGURES 5a-5h are representative *in situ* hybridization photomicrographs of GPCR expression in the mouse brain. FIGURE 5a: GPR63 in the Ammons horn (CA) regions of the hippocampus. FIGURE 5b: PGR7 in the habenula. FIGURE 5c: GRCA in the cortex and thalamus. FIGURE 5d: GPR63 in the Purkinje cells of the cerebellum. FIGURE 5e: GPR37 in the frontal cortex. FIGURE 5f: GPR26 in the inferior olive. FIGURE 5g: GPR50 in the cells lining the third ventricle. FIGURE 5h: PGR15 in the preoptic region of

the hypothalamus. Vertical lines on sagittal mouse brain drawing represent approximate coronal plane of photomicrographs. Scale bars = 500 μ m.

FIGURES 6a-6b. Home Cage Activity data for GPR85. Figure 6A. illustrates the average 24 hour activity of GPR85 wild type and knock out female mice. Figure 6B illustrates the average 24 hour activity of GPR85 wild type and knock out male mice.

FIGURES 7a-7b. Temperature differences between GPR85 knock out and wild type mice. Figure 7A. SIH results showing an increased body temperature change for knock out compared to wild type mice. Figure 7B. Baseline core body temperature difference between wild type and knock out mice.

FIGURE 8. Percentage freezing in the conditioned fear test. GPR85 knock out mice displayed significantly more freezing responses during the context test.

FIGURES 9a-9b. Acute effects of ethanol-induced hypothermia. Figure 9A. Initial sensitivity to the hypothermic effects of ethanol as measured by the difference before and 30 minutes after an i.p injection of 2.5 g/kg ethanol on two consecutive treatment days.

GPR85 knock out mice display a decreased initial sensitivity to the effects of ethanol.

Figure 9B. Tolerance to the hypothermic effects of ethanol as shown by the difference in the change of core body temperature for day 1 and day 2.

Detailed Description of the Invention

G protein coupled receptors (GPCRs) include receptors for neurotransmitters, light, odors, hormones, and molecules used for communication in the immune system. GPCRs are by far the largest family of receptors known. It is believed that there are as many as 1,000 different GPCRs for odor recognition alone.

Identification of GPCR Polypeptides and Polynucleotides

To identify the full complement of GPCRs in human and mouse, we embarked on a multi-step process; the first step was to identify previously known GPCR genes and then the subsequent identification of novel genes. To identify known genes we searched the public literature and sequence databases of the National Center for Biotechnology Information for

human and mouse GPCRs and then performed sequence comparisons. This procedure defined a unique gene set of GPCRs for both human and mouse and identified the human and mouse orthologs. In total, 340 GPCRs were identified in human and 304 in mouse. Sequence alignments indicated that 260 of these molecules were common to both species (Fig. 1).

We then asked whether the remaining GPCR genes (80 human and 44 in mouse), which did not show a counterpart in the other species, might have undiscovered orthologs. Using the non-shared GPCRs as queries, the public human and mouse genome sequence databases were searched for orthologous genes using TBLASTN, a variation of the Basic Local Alignment Search Tool (BLAST). These studies identified mouse orthologs for 61 of the human GPCRs, but no orthologs could be found for the remaining 19 (Fig. 1). No human orthologs were detected for 43 of the mouse genes. Thirty-three of these mouse genes belonged to the trace amine and MAS-related gene families. In combination with the literature/database searches, these studies for orthologs increased the number of GPCRs to 342 in human and 366 in mouse, with 323 GPCRs shared by the two species (Fig. 1).

We subsequently undertook an exhaustive search for new human GPCR genes. Two different approaches were used. In the first, we employed a homology-based strategy to search the human genome sequence database for genes encoding GPCRs (<http://genome.ucsc.edu/goldenPath/14nov2002/chromosomes/>). Two hundred fifty-four known GPCRs, representative of all classes, were each used as an independent query in TBLASTN searches of all human chromosomes. These searches yielded ~500,000 matches, which were first reduced to ~50,000 unique matches and then to 10,000 matches with homology to known GPCRs (see Methods). Among these, hits representing 315 of the 342 known GPCR genes were detected, consistent with 90% - 95% coverage of the human genome database. Approximately 1000 hits were homologous to chemosensory GPCR receptors. Continued analysis of the remaining hits revealed 25 novel GPCR genes.

In a second discovery method, a search was conducted for proteins with sequence motifs characteristic of the four different classes of GPCRs. The Hidden Markov Model (HMM) profile-based approach was used to search the human proteome. This method yielded 1,100 potential matches. Among these hits 331 of the 342 known GPCRs were

represented, confirming the validity of the search strategy. Following elimination of known genes, three novel genes were identified. The combination of both genomic search strategies revealed 28 GPCR genes that have not been previously described. These genes are referred to as PGR1 to PGR28 (Fig.1). Searches of the mouse genome sequence database, together with RT-PCR analyses, identified orthologs for 25 of the 28 novel genes in the mouse.

Altogether, these searches identified a total of 383 GPCRs in human and 391 in mouse; 358 of the GPCRs were common to the two species.

10 Methods

The 254 GPCRs used as queries were aligned using the Clustal W program. The amino acid sequence of the seven-transmembrane region of each GPCR was extracted and used to search through the public human genome (HG) database (downloaded in August, 2001) using TBLASTN at an E-value of 10. The resulting hits (~500,000) were combined and sorted according to contig and position numbers. Only the hit with the best E-value was selected among the group of hits within 1kb from each other on the same contig. Each of the ~50,000 unique hits generated were used to search against nr protein database using BLASTP. From this search, 10,000 hits appeared to be most homologous to GPCRs. Almost 2000 of these hits were determined to be parts of various known GPCRs and were excluded from further consideration. The best 500 of the remaining hits were subjected to full-length gene structure prediction. This process involved comparison of 200kb genomic DNA sequence surrounding each hit with the full-length sequence of its most homologous known GPCR using BLAST2. Twenty-five candidate novel GPCRs were obtained. Their nucleotide sequences were then used to search the EST database for the identification of human and/or mouse ESTs.

For the HMM profile-based approach, GPCR Class A, B and C HMM models were downloaded from the Pfam database and were used as queries in the HMMSEARCH program (HMMER package) to search against the International Protein Index (IPI) proteome database. All hits with E-values of less than 0.01 were evaluated for the existence of 7 TM domains using the HMMTOP program. Full-length coding sequences were

predicted through a combination of methods including EST sequence assembly, ORF Finder, GenomeScan, GeneWise and GeneScan programs.

GPCRs from the same class were aligned to the class specific HMM model using the HMMALIGN program of the HMMER package. Positions not aligned to matching sites in the HMM model were removed. These multiple alignments were used to build neighbor-joining phylogenetic trees by the ClustalW program. Gaps and multiple substitutions were not corrected. Bootstrap consensus trees were plotted using TreeView. They were rooted using GPCRs that did not fit into any of four known classes. Bootstrap values for nodes near the root of the Class A tree were very low (<10%), reflecting the distant homology of the different families in this class.

Phylogenetic Analysis

Phylogenetic and receptor-ligand relationships among the GPCRs were subsequently analyzed. Each human and mouse GPCR was first assigned to one of the four distinct classes of GPCRs (A, B, C, F/S) by comparing with HMM models. All but five of the receptors (TPRA40, TM7SF1, TM7SF1L1, TM7SF1L2 and TM7SF3) could be assigned to one of the four classes by this method. These assignments indicate that of 370 human GPCRs, 287 belong to Class A, 50 to Class B, 17 to Class C, and 11 to Class F/S. Of 393 mouse GPCRs, 311, 50, 17, and 10 belong to Classes A, B, C, and F/S, respectively.

The GPCRs were next catalogued according to ligand specificities reported in the literature. This effort identified 229 human and 215 mouse GPCRs with known ligands. The remaining 145 human and 178 mouse GPCRs have no known ligands and are therefore orphan receptors. Among the orphan receptors, 100 human and 133 mouse receptors belong to Class A, 34 human and 34 mouse receptors to Class B, 6 human and 6 mouse receptors to Class C, none to Class F/S, and 5 human and 5 mouse receptors could not be assigned to a specific class (Fig. 1).

The GPCRs were subsequently divided into a series of families of related receptors that either recognize the same/similar ligand(s) or are highly likely to do so. Sequence comparisons and phylogenetic analyses (see below) showed that GPCRs with highly related ligand specificities that are traditionally classed as belonging to the same "family" are at

least 40% homologous in protein sequence. We therefore assigned GPCRs to specific families using the criteria that members of a family either recognize the same/similar ligand or show at least 40% sequence homology. In this manner, 93 different families of GPCRs were identified, including 16 families of orphan receptors that have not been previously described (Fig. 1). These studies assigned 12 of 145 human and 47 of 178 mouse orphan GPCRs to seven different families of receptors that interact with known ligands. The orphan receptors in these families can be predicted to recognize ligands similar to those detected by other members of the same family.

To further investigate sequence-ligand relationships among human GPCRs, we conducted a phylogenetic analysis. GPCRs were aligned to the class specific HMM profile model using the HMMALIGN program of the HMMER package. These alignments were used for the construction of phylogenetic trees, using the Clustal W program. The phylogenetic trees were then overlaid with information on the ligand specificities of individual receptors, where available.

The combined phylogenetic/ligand analyses of human GPCRs are shown in Fig. 2. The phylogenetic tree of the class A receptors, the largest set, was composed of a number of major branches that were progressively subdivided into smaller branches containing increasingly related GPCRs. The three smaller classes of receptors (classes B, C, and F/S) exhibited a similar organization, but fewer branches. GPCRs that recognize the same ligand, such as receptors for the neurotransmitter acetylcholine, or receptors that belong to the same family, were clustered together in small branches.

The phylogenetic trees, in addition, revealed a striking, higher order organization relevant to GPCR functions. Multiple receptor families with related functions that recognize ligands of a particular chemical class were grouped in the same large branch. For example, the 40 neurotransmitter/neuromodulator receptors of the dopamine, serotonin, trace amine, adenosine, acetylcholine, histamine and adrenoreceptor α and β families were all clustered phylogenetically. Moreover, the 106 GPCRs known to recognize peptide ligands were clustered in four large branches, three in the class A tree and one in the class B tree. This organization is of predictive value for numerous orphan GPCRs. For example, GPCRs such as PGR2, PGR3, PGR11, GPR19, GPR37, GPR39, GPR45, GPR63 and

GPR103 could be predicted to have peptide ligands since they were grouped with other receptors activated by peptides. Other orphan receptors, such as GPR21 and GPR52 could conceivably be activated by amine neuromodulators, as they clustered phylogenetically with amine-type molecules in the large neurotransmitter branch of the class A tree.

5

Full-Length Sequence for Novel Human GPCR Genes

Methods

To identify full-length clones for the the novel human GPCR genes that were discovered by the gene-mining effort, the following methods were used:

10 First-Strand cDNA Synthesis

First strand cDNA Synthesis was performed as essentially described in the following kit, CLONTECH Laboratories, Inc., Protocol # PT3269-1 16 Version # PR14596.

Two 10- μ l reactions described below convert 50 ng–1 μ g of total or poly A+ RNA into RACE-Ready first-strand cDNA. For optimal results, use 1 μ g of poly A+ RNA or 1 μ g of total RNA in the reactions below.

15

1. Combined the following in separate 0.5-ml microcentrifuge tubes:

For preparation of 5'-RACE-Ready or cDNA 3'-RACE-Ready cDNA

20 1–3 μ l RNA sample 1–3 μ l RNA sample
 1 μ l 5'-CDS primer 1 μ l 3'-CDS primer A
 1 μ l SMART II A oligo

2. Add sterile H₂O to a final volume of 5 μ l for each reaction.
3. Mix contents and spin the tubes briefly in a microcentrifuge.
4. Incubate the tubes at 70°C for 2 min.
- 25 5. Cool the tubes on ice for 2 min.
6. Spin the tubes briefly to collect the contents at the bottom.
7. Add the following to each reaction tube (already containing 5 μ l):

30 2 μ l 5X First-Strand buffer
 1 μ l DTT (20 mM)
 1 μ l dNTP Mix (10 mM)
 1 μ l PowerScript Reverse Transcriptase
 10 μ l Total volume

8. Mix the contents of the tubes by gently pipetting.
 9. Spin the tubes briefly to collect the contents at the bottom.
 10. Incubate the tubes at 42°C for 1.5 hr in an air incubator.
 - 5 11. Dilute the first-strand reaction product with Tricine-EDTA Buffer:
 - Added 20 µl if started with < 200 ng of total RNA.
 - Added 100 µl if started with > 200 ng of total RNA.
 - Added 250 µl if started with poly A+ RNA.
 12. Heat tubes at 72°C for 7 min.
 - 10 13. Samples can be stored at -20°C for up to three months.
- Now have 3'- and 5'-RACE-Ready cDNA samples.

3' and 5' RACE

- 15 1. Treat total RNA or mRNA with calf intestinal phosphatase (CIP) to remove the 5' phosphates. This eliminates truncated mRNA and non-mRNA from subsequent ligation with the GeneRacer RNA Oligo. Dephosphorylation reaction was set up in a 1.5 ml sterile microcentrifuge tube using the reagents in the kit. 1-5 µg total RNA was used in a total volume of 10 µl with 10X RNaseOut and CIP (10 U). The reaction was incubated at 50°C
- 20 for 1 hour. After incubation, the RNA was precipitated with ethanol.

2. Treat dephosphorylated RNA with tobacco acid pyrophosphatase (TAP) to remove the 5' cap structure from intact, full-length mRNA. This treatment leaves a 5' phosphate required for ligation to the GeneRacer RNA Oligo.

The reaction was set up on ice the using the reagents in the kit.

- 25 Dephosphorylated RNA 7 µl
- 10X TAP Buffer 1 µl
- RNaseOut (40 U/l) 1 µl
- TAP (0.5 U/ul) 1 µl
- Total Volume 10 µl

- 30 The reaction was incubated at 37°C for 1 hour. After incubation, the RNA was

precipitated with ethanol.

3. Ligate the GeneRacer RNA Oligo to the 5' end of the mRNA using T4 RNA ligase. The GeneRacer RNA Oligo will provide a known priming site for GeneRacer. 7 µl of dephosphorylated, decapped RNA was incubated at 65°C for 5 minutes. Then the following were added:

10X Ligase Buffer 1 µl

10 mM ATP 1 µl

RNaseOut (40 U/ul) 1 µl

T4 RNA ligase (5 U/ul) 1 µl

10 Total Volume 10 µl

After incubation, 90 µl of DEPC treated water was added and the reaction was extracted with phenol/chloroform, and precipitated with the addition of 2 µl of 10 mg/ml mussel glycogen, 10 µl 3 M sodium acetate, pH 5.2 and 220 ul of 95% ethanol.

4. Reverse-transcribe the ligated mRNA using Cloned AMV RT or SuperScript II RT and the GeneRacer. OligodT Primer to create RACE-ready first-strand cDNA with known priming sites at the 5' and 3' ends.

To 10µl ligated mRNA, 1 µl of the desired primer was added and 1 µl of dNTP Mix (25 mM each) to the ligated RNA. Then the mixture was incubated at 65°C for 5 minutes to remove any RNA secondary structure, chilled on ice for 2 minutes and added the following reagents to the ligated RNA and primer mixture:

5X RT Buffer 4 µl

Cloned AMV RT (15 U/µl) 1 µl

Sterile water 2 µl

RNaseOut (40 U/µl) 1 µl

25 Total Volume 20 µl

The reaction was incubated at 45°C for 1 hour and then at 85°C for 15 minutes to inactivate the cloned AMV RT.

5. To obtain 5' ends, amplify the first-strand cDNA using a reverse gene specific primer (Reverse GSP) and the GeneRacer 5' Primer. Only mRNA that has the GeneRacer

RNA Oligo ligated to the 5' end AND is completely reverse-transcribed will be amplified using PCR. If needed, perform additional PCR with nested primers.

6. To obtain 3' ends, amplify the first-strand cDNA using a forward gene-specific primer (Forward GSP) and the GeneRacer 3' Primer. Only mRNA that has a polyA tail and is reverse-transcribed will be amplified using PCR. If needed, perform additional PCR with nested primers.

PCR conditions used for 3' or 5' RACE or internal fragment amplification

- PCR was performed using the following cycle parameters, 94C for 2 minutes for melting, then (94C for 30 sec; 67C for 1 minute; 72C for 1.5 minutes) for 6 cycles, then (94C for 30 seconds, 60C for 1 minute, 72C for 1.5 minutes) for 38 cycles, then 72C for 7 minutes and then hold at 4C.

7. Purify RACE PCR products using the S.N.A.P. columns included in the kit.

15 Rapid Amplification of cDNA Ends (RACE)

This procedure describes the 5'-RACE and 3'-RACE PCR reactions that generate the 5' and 3' cDNA fragments.

1. For each 50- μ l reaction, mix the following reagents:

- 20 34.5 μ l PCR-Grade Water
 5 μ l 10X Advantage 2 PCR Buffer
 1 μ l dNTP Mix (10 mM)
 1 μ l 50X Advantage 2 Polymerase Mix
 41.5 μ l Total volume

25

Mix well by vortexing (without introducing bubbles) and briefly spin the tube in a microcentrifuge.

2. For 5'-RACE: PCR reactions as shown in Table III of Clontech's RACE kit.

For 3'-RACE: PCR reactions as shown in Table IV of Clontech's RACE kit.

PCR Cycle conditions: as described in the Clontech's RACE kit.

Complete reactions were then run on gel to visualize PCR products. If the gel showed nothing then the reaction would be amplified for additional cycles (total of 40).

5 Human PGR4

Full length cDNA was isolated from human Pituitary by a combination of 5' and 3' Rapid Amplification of cDNA Ends (RACE) and internal RT-PCR experiments using the methods described above. RACE pituitary was prepared using the Invitrogen GeneRacer Kit (Cat # L1500-01).

10

The following RACE primers were used:

5' RACE (Invitrogen) CGACTGGAGCACGAGGACACTGA (SEQ ID NO: 1545)

3' RACE (Invitrogen): GCTGTCAACGATACGCTACGTAACG (SEQ ID NO: 1546)

15 5' nested RACE primer: GGACACTGACATGGACTGAAGGAGTA (SEQ ID NO: 1547)

3' nested RACE primer: CGCTACGTAACGGCATGACAGTG (SEQ ID NO: 1548)

The following cDNA primers were used:

20 HPG5dn01, GCCGCGCTGCAGGTGCACGATG, (SEQ ID NO: 1549)
 HPG5-360up, TGCCACCTGCTCTTCTACGTGATG, (SEQ ID NO: 1550)
 HPG5-601dn GCAAATCAGTGTGCAAATCGAAA, (SEQ ID NO: 1551)
 HPG5-629up CATTCCTGGAGAGATCTCGTGGGA (SEQ ID NO: 1552)
 HPG5-1183dn GGTGCCACTGATGGAGGGTACTG, (SEQ ID NO: 1553)
 25 HPG5-755up GGTAAGCCTGGCCTACTCGGAGAG, (SEQ ID NO: 1554)
 HPG5MaxDN TGCACCTGGCCAACAAATCCTTTT, (SEQ ID NO: 1555)
 HPG5MaxUP GGTAAGCCTGGCCTACTCGGAGAG, (SEQ ID NO: 1556)
 HPGgMax5up18 GGGCCAGAGGCGAGATGT, (SEQ ID NO: 1557)
 HPG5gMax5dn GCAGGTCCGCGCAGAA, (SEQ ID NO: 1558) used for 5' RACE
 30 HPG5gMax3up CCACCAGATCCGCGTGTC; (SEQ ID NO: 1559) used for 3'

RACE

HPG5gMax3end GTTGGTCAGGTTGGTCTCGAAC, (SEQ ID NO: 1560)

PGR4 cDNA sequence (SEQ ID NO: 88)

5 ATGGACTCATTACAAGTTGTTTTAGGATCTACCTCCAGACCCATGGAGTTTCTTT
AGTAAAGCCTGAACGACACAGGCCAAAATAATCTCCAAAGGCCAGCTCTGACC
CTTTTAAATCAATTTTAGCTAAATCCGTTTACAAAAGGCTTCGCACATCCAGTGT
CCCTGAAAAATAAAGGAGGTTGGGCAGGCCCTGCGGGGGCTCGAGGAATTCGC
TAAGTGAGTTTTCTGGCTTCTGGATACACTTTCAAAGGGCCAGAGGGCACGAGG
10 CTTCGCGCTTGGCCGCCACCTCCCCGGCCAGCTGCGGTGTTTCGCGGCCAGTGTT
GCCGGGCACTTCCTGGTTCCCGCGCGCCCCGGGTGCAGCTCCCTGCACCCAGTG
CTGGCGCTCCTCAGAAGGGAGGGGGCCAGAGGCGAGATGTCGCAACCGCCTCC
CTCCCTCTTTCCCGCCTTGGCACTCAGTCGCCTCCAGATGAGCACTCTCTCAG
ACCGCTGCGGGCCGCCAGGCGCCGGGAATGTCCCCTGAATGCGCGCGGGCAGC
15 GGGCGACGCGCCCTTGCGCAGCCTGGAGCAAGCCAACCGCACCCGCTTTCCCTT
CTTCTCCGACGTCAAGGGCGACCACCGGCTGGTGCTGGCCGCGGTGGAGACAA
CCGTGCTGGTGCTCATCTTTCAGTGTGCTGCTGGGCAACGTGTGCGCCCTGG
TGCTGGTGGCGCGCCGACGACGCCGCGGCGCGACTGCCTGCCTGGTACTCAACC
TCTTCTGCGCGGACCTGCTCTTCATCAGCGCTATCCCTCTGGTGCTGGCCGTGCG
20 CTGGACTGAGGCCTGGCTGCTGGGCCCCGTTGCCTGCCACCTGCTCTTCTACGT
GATGACCCTGAGCGGCAGCGTCACCATCCTCACGCTGGCCGCGGTCAGCCTGGA
GCGCATGGTGTGCATCGTGACCTGCAGCGCGGCGTGCGGGGTCTGGGCGGC
GGGCGCGGGCAGTGCTGCTGGCGCTCATCTGGGGCTATTCGGCGGTCGCCGCTC
TGCCTCTCTGCGTCTTCTTCCGAGTCGTCCCGCAACGGCTCCCCGGCGCCGACCA
25 GGAAATTTTCGATTTGCACACTGATTTGGCCCACCATTCTGGAGAGATCTCGTG
GGATGTCTCTTTTGTACTTTGAACCTTCTGGTGCCAGGACTGGTCATTGTGATC
AGTTACTCCAAAATTTTACAGATCACAAAGGCATCAAGGAAGAGGCTCACGGT
AAGCCTGGCCTACTCGGAGAGCCACCAGATCCGCGTGTCCCAGCAGGACTTCCG
GCTCTTCCGCACCCTCTTCTCCTCATGGTCTCCTTCTTCATCATGTGGAGCCCC
30 ATCATCATCACCATCCTCCTCATCCTGATCCAGAACTTCAAGCAAGACCTGGTC
ATCTGGCCGTCCCTCTTCTTCTGGGTGGTGGCCTTCACATTTGCTAATTCAGCCC
TAAACCCCATCCTCTACAACATGACACTGTGCAGGAATGAGTGGAAGAAAATTT
TTTGCTGCTTCTGGTTCCTCAGAAAAGGGAGGCCATTTTAAACAGACACATCTGTCA
AAAGAAATGACTTGTGATTATTTCTGGCTAATTTTTCTTTATAGCCGAGTTTCT
35 CACACCTGGCGAGCTGTGGCATGCTTTTAAACAGAGTTTCAATTTCCAGTACCCTC
CATCAGTGCACCCTGCTTTAAGAAAATGAACCTATGCAAAATAGACATCCACAGC
GTCGGTAAATTAAGGGGTGATCACCAAGTTTCATAATATTTTCCCTTTATAAAA
GGATTTGTTGGCCAGGTGCAGTGGTTCATGCCTGTAATCCCAGCAGTTTGGGAG
GCTGAGGTGGGTGGATCACCTGAGGTGAGGAGTTCGAGACCAACCTGACCAAC
40 ATGGTGAGACCCCGTCTCTACTAAAAATAAAAAAAAAAATTAGCTGGGAGTG
GTGGTGGGCACCTGTAATCCTAGCTACTTGGGAGGCTGAACCAGGAGAATCTCT
TGAACCTGGGAGGCAGAGGTTGCAGTGAGCCGAGATCGTGCCATTGCACTCCA
ACCAGGGCAACAAGAGTGAAACTCCATCTT

PGR4 polypeptide sequence (SEQ ID NO: 87)
 MSPECARAAGDAPLRSLEQANRTRFPFFSDVKGDHRLVLA AVETTVLV LIFAVSLL
 5 GNVCALVLVARRRRRGATACLVNLFCADLLFISAIPLVLAVRWTEAWLLGPVAC
 HLLFYVMTLSGSVTILTLAAVSLERMVCIVHLQRGV RGPGRRARAVLLALIWG YSA
 VAALPLCVFFRVVPQRLPGADQEISICTLIWPTIPGEISWDVSFVTLNFLVPGLVIVIS
 YSKILQITKASRKRLTVSLAYSESHQIRVSQQDFRLFRTLFLLMVSFFIMWSPHITILLI
 LIQNFKQDLVIWPSLFFWVVAFTFANSALNPILYNMTLCRNEWKKIFCCFWFPEKG
 10 AILTDTSVKRNDLSIISG

Human PGR2

Full length cDNA was isolated from human uterus by a combination of 5' and 3'

15 Rapid Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as
 described above. RACE pituitary was prepared using the Invitrogen GeneRacer Kit (Cat #
 L1500-01).

The following RACE primers were used:

20 5' RACE (Invitrogen) CGACTGGAGCACGAGGACACTGA (SEQ ID NO: 1545)
 3' RACE (Invitrogen): GCTGTCAACGATACGCTACGTAACG (SEQ ID NO:
 1546)
 5' nested RACE primer: GGACACTGACATGGACTGAAGGAGTA (SEQ ID NO:
 1547)
 25 3' nested RACE primer: CGCTACGTAACGGCATGACAGTG (SEQ ID NO: 1548)

The following cDNA primers were used:

3RaceUp ACTACCTTCTGGCGCTCACA (SEQ ID NO: 1561)
 5RaceDn CCCAGCAGGACACTGTAGTAGA (SEQ ID NO: 1562)
 30 HPG9-1up ATGGATCCCAGCGTTGTTAGCAAT (SEQ ID NO: 1563)
 HPG9-1dnA TGGAGTCCTTGGATGGCCTTATTC (SEQ ID NO: 1564)
 HPG9-1dnB CCGCGAACACGATGACCAC (SEQ ID NO: 1565)
 HPG9-2upB GGGGGAAGCTGGGACCTCCGAATA (SEQ ID NO: 1566)
 HPG9-3up CGAGGTCCTCAAGTGGGCTCACT (SEQ ID NO: 1567)

HPG9-3dn GGTGTTTCTATGGCGCGATCTCA (SEQ ID NO: 1568)

HPG9-MaxUp CGTTGTAGCAATGAGTATTATG (SEQ ID NO: 1569)

HPG9-Maxdn TATCACTTTATTTTATTAAAGGTTACAC (SEQ ID NO: 1570)

5 PGR2 cDNA sequence (SEQ ID NO: 34)
ATGAGCCCAGGAGCTCGAGACCAGCCTAGGCAACATGGCGAAACACCGTCTCT
ACAAAAAATACGAAAATTAGCTGGGCGTGTTGGTGCTTGCCTGTAATGCCAGCT
ATTTGGGAGGCTGAGATGGGAGGATCACTTGAGCCTGGGAGTTCGAGGCTGCA
GTGAGCTATGATCACACCACTGTACCACAGCCTGGGTGACAGAGTGAGACCCT
10 GTCTTGAGGGGTAGGGAGGCAGAAGGAAAAAAGAGAGAGAGAGACCCTGG
TGCTCAGGCCTGGTGGCTCTGGCTGGACTGATCAGGGCTGAAGACTTCAGAGAC
CAAAAAGGTCAAGGTGTGGCCGGGTGCGGTGGCTCACACCTGTGATCCCAGCA
TTTTTGGGAGACCCAGGTGGGCATATCACCTGAGGCCAGGAGCTCAGGACCAG
CCTGGCTAACACGGTGAAACCCCGTCTCTACTAAAAATACAAAAATTAGCCAG
15 GCATGGTGGCAGGCACCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAGGAGA
ATCACTGGAACCCAGGAGGCAGAGGTTGCAGTGAGCCGAGATAGCACCATTGC
ACTCCAGCCTGGGTGACAGAGCGAGACTCTGTCTCAAAAAGAAAAGAAAAAA
AAGTCAAGGTGTGCGGCTGGGTCTTCATAACATCTTTCACCTTGCCAGGCTGG
CTCAGAGGTGACTGCCTTAGTGGATAGGATCCCTTCCACCGTGGGCTAGCAGCC
20 TACCCTGGTCACTGACACCACACCATGTAGGAAAGAATCGCCACCACCAAGAA
GGGGCCTCTCACCTCTGTATAGGCTGTGTGCTGGCTGATGACGTGGTTGCCCTG
TCCTGTCTGCTGCTGCCACTGAGCTGGACATCTCCAGGCTCCATCTCTTGAACCA
TGGATCCCAGCGTTGTAGCAATGAGTATTATGATGTTGCCCATGGAGCAAAAG
ATCCAGTGGTCCCCACTTCCCTGCAGGACATCACTGCTGTCCTGGGTACAGAAG
25 CATATACTGAGGAAGACAAATCAATGGTGTCCCATGCACAGAAAAGCCAGCAT
TCTTGTCTCAGCCATTCCAGGTGGCTGAGGTCTCCACAGGTCACAGGGGGAAGC
TGGGACCTCCGAATAAGGCCATCCAAGGACTCCAGCAGTTTCCGCCAGGCTCAG
TGTCTGCGTAAGGATCCTGGGGCAAACAACCACTTGGAGAGCCAAGGGGTGAG
AGGTACAGCTGGCGATGCTGACAGGGAGCTGCGGGGACCCTCAGAAAAAGCCA
30 CAGTCAGCCTCCTGACCGCAGTGGCCCTGGCGCGCCTTGCCACCAGGACCAGGA
GGCCCTCCTACTACTACCTTCTGGCGCTCACAGCCTCGGATATCATCATCCAGGT
GGTCATCGTGTTGCGGGGCTTCCTCCTGCAGGGAGCAGTGCTGGCCCGCCAGGT
GCCCCAGGCTGTGGTGCGCACGGCCAACATCCTGGAGTTTGCTGCCAACCACGC
CTCAGTCTGGATCGCCATCCTGCTCACGGTTGACCGCTACACTGCCCTGTGCCA
35 CCCCCTGCACCATCGGGCCGCCTCGTCCCCAGGCCGGACCCGCCGGGCCATTGC
TGCTGTCCTGAGTGCTGCCCTGTTGACCGGCATCCCCTTCTACTGGTGGCTGGAC
ATGTGGAGAGACACCGACTACCCAGAACACTGGACGAGGTCCTCAAGTGGGC
TCACTGTCTCACTGTCTATTTTCATCCCTTGTGGCGTGTTCTGGTCACCAACTCG
GCCATCATCCACCGGCTACGGAGGAGGGGCGGAGTGGGCTGCAGCCCCGGGT
40 GGGCAAGAGCACAGCCATCCTCCTGGGCATCACCACACTGTTACCCTCCTGTG
GGCGCCCCGGGTCTTCGTGCTGCTCTACCACATGTACGTGGCCCTGTCCACCG
GACTGGAGGGTCCACCTGGCCTTGATGTGGCCAACATGGTGGCCATGCTCCA
CACGGCAGCCAACCTTCGGCCTCTACTGCTTTGTGAGCAAGACTTTCGGGGCCAC

TGTCGGACAGGTCATCCACGATGCCTACCTGCCCTGCACTTTGGCATCACAGCC
 AGAGGGCATGGCGGCGAAGCCTGTGATGGAGCCTCCGGGACTCCCCACAGGGG
 CAGAAGTGTAGAGGAGGGGGCCAGCTAGGGAGCTCAGGGTGGCTCATGGCCA
 CATGTACTGGGGCCTTTGAGGTTGTACCCAAAACACGTTTATCAACAGCTTGCT
 5 TTCCTTGGGTGGGGGTGGAGGCTCCTCCTTTGGGTGTGGCTCCCAGGTAGAGAG
 GAGGACAACCTTAGCCAGCTCTTATGTTTGCTTCACCAGCAATCCCTATTTCCTGG
 GAAGATGAAAGGGCACTGCCAGGCACAGGCTAATAGCATCAGTGCTGTGGGCA
 TTCCTTTGCGGGGGGCATTTTGCCTGGCTCATCGTGAATGCCAGATTAATGTTGG
 TTGAATGGATAGAAAAACGGACAGATGGAGGCCNGGGTGGCGGTGGCTCACGCC
 10 TGTAATCCCAGCACGTTGGGAGGCTGAGGCAGGCGGATCACGAGGTCAGGAGA
 TCGAGACCACAGTGAAACCCTGTCTCTACTAAAAATACAAAAAATTAGCTGGA
 CGCAGTGGCGGGCGCCTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGAA
 TGGCGTGAACCCGGAAGGCGGAGCTTGCGGTGAGCCGAGATCCCGCCACTGCA
 CTCCAGCCTGGGCGACAGAGTGAGACTCCGTCTCA

15 PGR2 polypeptide sequence (SEQ ID NO: 33)
 MDPSVVSNEYDVAHGAKDPVVPTSLQDITAVLGTEAYTEEDKSMVSHAQKSQHS
 CLSHSRWLRSPQVTGGSWDLRIRPSKDSSSFRQAQCLRKDPGANNHLESQGVRGTA
 GDADRELGRPSEKATVSLTAVALARLATRTRRPSYYLLALTASDIIIQVVIVFAGF
 20 LLQGAVLARQVPQAVVRTANILEFAANHASVWIAILLTVDRYTALCHPLHHRAASS
 PGRTRRAIAAVLSAALLTGIPFYWWLDMWRDTSRPTLDEV LKWAHCLTVYFIPC
 GVFLVTNSAIIHRLRRRGRSGLQPRVGKSTAILLGITTLFTLLWAPRVFVMLYHMYV
 APVHRDWRVHLALDVANMVMAMLHTAANFGLYCFVSKTFRATVRQVIHDAYLPCT
 25 LASQPEGMAAKPVMPEPPGLPTGAEV

Human PG3

Full length cDNA was isolated from human whole brain by a combination of 5' and
 3' Rapid Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as
 30 described above. RACE pituitary was prepared using the Invitrogen GeneRacer Kit (Cat #
 L1500-01).

The following RACE primers were used:

| | |
|--------------------------|---|
| 5' RACE (Invitrogen) | CGACTGGAGCACGAGGACACTGA (SEQ ID NO: 1545) |
| 35 3' RACE (Invitrogen): | GCTGTCAACGATACGCTACGTAACG (SEQ ID NO: 1546) |
| 5' nested RACE primer: | GGAACTGACATGGACTGAAGGAGTA (SEQ ID NO: 1547) |
| 3' nested RACE primer: | CGCTACGTAACGGCATGACAGTG (SEQ ID NO: 1548) |

The following cDNA primers were used:

| | | |
|----|-----------------|--|
| | Hpg10max5up | ATGGAGCACACGCACGCCCACCTCG (SEQ ID NO: 1571) |
| | Hpg10max5dn | TCATGATGATGCGGGGGGCCAAAG (SEQ ID NO: 1572) |
| 5 | Hpg10-02up | CGGCCAAGGGTAGGAGCCAGTCCTG (SEQ ID NO: 1573) |
| | Hpg10-02dn | CTTGAGCGGGTGGCAGACAGCGATA; (SEQ ID NO: 1574) |
| | used in 5' RACE | |
| | Hpg10-03up | GGGTTTCGTGCCCCGTGGTCTACT (SEQ ID NO: 1575) |
| | Hpg10-03dn | ATGGTGAACAAGATGGCGGTGGT (SEQ ID NO: 1576) |
| 10 | Hpg10-04up | CACCCGCTCAAGTACCACA (SEQ ID NO: 1577) |
| | Hpg10-04dn | TCACAGGATGATGACACAAGCTC (SEQ ID NO: 1578) |
| | Hpg10-05up | CCATCTTGTTACCATACCTC, (SEQ ID NO: 1579) used in 3' |
| | RACE | |
| | Hpg10-05dn | CATTACGACTTTTTATAGGTTTTCC (SEQ ID NO: 1580) |
| 15 | Hpg10g01up | CACCGAGCCGGCGACCAGAGTC (SEQ ID NO: 1581) |
| | Hpg10g01dn | TGAGCGGGTGGCAGACAGCGAT (SEQ ID NO: 1582) |

PGR3 cDNA sequence (SEQ ID NO: 54)

| | |
|----|--|
| | CTGCATCTTCTCCCCTGAAAGTGGAGCCAAGCGAGGCGGCTGGGACCCCCCTCCT |
| 20 | CTTCCGCATCCCTCCCACCCACACACACTCCGCTTCCAGGCAGCCGCTGATTG |
| | GCTGCGGGGAGCGGCGTCCCAGCCCCCGGCTTTGAGGCGGGAGTGGAGCGGG |
| | TCCGAGGTGGGAGGCGCACAGACGGGCTCCGGGAGCCCCCTCCCGAGGCCCCGC |
| | GCAGCGCGCCCCGCACCCTGCGCCCCGCGCCCTGCGGGAGGGCTGAGCCAAGA |
| | CTCCAGGCGGGCAGGTGCGGAGCGAGCAGAGGGGATCACGGCCAAGGGTAGG |
| 25 | AGCCAGTCCTGCGGGGAGAGAGGCGCTGCTGCTCCAGCTGCCGCTGCCTCCGCC |
| | GCCGCCACCACCGAGCCGGCGACCAGAGTCGGGCTGGCAGGCCGGGCGCGAAG |
| | CGGCAAGGGGAGCGAGGGGCGCGCTCATGGAGCACACGCACGCCACCTCGCA |
| | GCCAACAGCTCGCTGTCTTGTTGGTCCCCCGGCTCGGCCTGCGGCTTGGGTTTC |
| | GTGCCCCGTGGTCTACTACAGCCTCTTGCTGTGCCTCGGTTTACCAGCAAATATCT |
| 30 | TGACAGTGATCATCCTCTCCCAGCTGGTGGCAAGAAGACAGAAGTCCTCCTACA |
| | ACTATCTCTTGGCACTCGCTGCTGCCGACATCTTGGTCCTCTTTTTCATAGTGTTT |
| | GTGGACTTCCTGTTGGAAGATTTTCATCTTGAACATGCAGATGCCTCAGGTCCCC |
| | GACAAGATCATAGAAGTGCTGGAATTCTCATCCATCCACACCTCCATATGGATT |
| | ACTGTACCGTTAACCATTGACAGGTATATCACTGTCTGCCACCCGCTCAAGTAC |
| 35 | CACACGGTCTCATACCCAGCCCGCACCCGGAAAGTCATTGTAAGTGTTTACATC |
| | ACCTGCTTCCTGACCAGCATCCCCTATTACTGGTGGCCCAACATCTGGACTGAA |

GACTACATCAGCACCTCTGTGCATCACGTCCTCATCTGGATCCACTGCTTCACCG
 TCTACCTGGTGCCCTGCTCCATCTTCTTCATCTTGAACCAATCATTGTGTACAA
 GCTCAGGAGGAAGAGCAATTTTCGTCTCCGTGGCTACTCCACGGGGAAGACCA
 CCGCCATCTTGTTACCATTAACCTCCATCTTTGCCACACTTTGGGCCCCCGCAT
 5 CATCATGATTCTTTACCACCTCTATGGGGCGCCCATCCAGAACCGCTGGCTGGT
 ACACATCATGTCCGACATTGCCAACATGCTAGCCCTTCTGAACACAGCCATCAA
 CTTCTTCCTCTACTGCTTCATCAGCAAGCGGTTCCGCACCATGGCAGCCGCCAC
 GCTCAAGGCTTTCTTCAAGTGCCAGAAGCAACCTGTACAGTTCTACACCAATCA
 TAACTTTTCCATAACAAGTAGCCCTGGATCTCGCCGGCAAACCTCACACTGCAT
 10 CAAGATGCTGGTGTACCAAGTATGACAAAAATGGAAAACCTATAAAAGTATCCC
 CGTGATTCCATAGGTGTGGCAACTACTGCCTCTGTCTAATCCATTTCAGATGG
 GAAGGTGTCCCATCCTATGGCTGAGCAGCTCTCCTTAAGAGTGCTAATCCGATT
 TCCTGTCTCCCGCAGACTGGGCAATTCTCAGACTGGTAGATGAGAAGAGATGGA
 AGAGAAGAAAGGAGAGCATGAAGCTTGTTTTACTTATGCATTTATTTCCACAG
 15 AGTCGTAATGACAGCAAAAGCTCCTACCAGTTTGAAGATGCCATTGGAGCTTGT
 GTCATCATCCTGTGACCAGTTAGGACACAAAGTAGAGAAGTAGTCTGTGATTTT
 GCCCTGGTACCATCCACAGTCACTGGGAACCCTTCATTTATGGGACTTACCAAG
 CCCAGTAGCACATAGCTGAGCCTGCACTCTTCTCCGAGAGCTGAGGTCATT
 ATCACTTCCCTCTGCTGTTCCCAGGAGCTAACAATAATGACTATTTTCAGGATTTT
 20 TTTCAAGGTGCCCTTTGTCTAGAGAGGGTGTGGTCTTGAATTGGCTCTGGCAC
 TCCTAGCTTCAGAATGACACTGTGGGAATAGAAGAGTATTGGATCCCATCCAAA
 CTGTGGCCAGAGCTTCTTCAGGAAATCTCCAAACCCGCATAGCTGTGACCTCAA
 ACCTGGGGTCTAAAAGGCAGTTTTCTATTTATCATTATGTATAGATTTTCTCTAT
 CTCCTCCAAAACAAAGACCCTGCCTGGTGCGCAGGGGGAAGGAGGAATTCTC
 25 GAGCCC

PGR3 polypeptide sequence (SEQ ID NO: 53)
 MEHTHAHLAANSSLSWWSPGSACGLGFVPVVYYSLLLCLGLPANILTVIILSQLVA
 RRQKSSYNYLLALAAADILVLFVIFVDFLLEDFILNMQMPQVPDKIIEVLEFSSIHTS
 30 IWITVPLTIDRYITVCHPLKYHTVSYPARTRKVIVSVYITCFLTSIPYYWWPNIWTE
 YISTSVHHVLIWIHCFTVYLVPCSIFFILNSIIVYKLRRKSNFRLRGYSTGKTTAILFTIT
 SIFATLWAPRIIMILYHLYGAPIQNRWLHIMSDIANMLALLNTAINFFLYCFISKRFR
 TMAAATLKAFFKCQKQPVFYTNHNFSITSSPWISPANSHCIKMLVYQYDKNGKPI
 KVSP

35

Human PGR6

Full length cDNA was isolated from human whole brain by a combination of 5' and
 3' Rapid Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as
 described above. RACE pituitary was prepared using the Invitrogen GeneRacer Kit (Cat #
 40 L1500-01).

The following RACE primers were used:

- 5' RACE (Invitrogen) CGACTGGAGCACGAGGACACTGA (SEQ ID NO: 1545)
 3' RACE (Invitrogen): GCTGTCAACGATACGCTACGTAACG (SEQ ID NO: 1546)
 5' nested RACE primer: GGACACTGACATGGACTGAAGGAGTA (SEQ ID NO: 1547)
 3' nested RACE primer: CGCTACGTAACGGCATGACAGTG (SEQ ID NO: 1548)

The following cDNA primers were used:

- ET11-01up ATGGGGGATGAGCTGGCACCTTG (SEQ ID NO: 1583)
 10 ET11-01dn TGGCACGGGGAAGCATCATGAGT (SEQ ID NO: 1584)
 ET11-02up TAGTTCCAGACAGCTGCTCCTTCCTTT (SEQ ID NO: 1585)
 ET11-02dn GAAGTCTTGGCCTCTGCATAGATCCTC (SEQ ID NO: 1586)
 ET11-03up ATGGTGGCAGTGGGATGATCTGTTA (SEQ ID NO: 1587)
 ET11-03dn AGGTAGCGCAGTGGATGGATGACT; (SEQ ID NO: 1588) used in 5'
 15 RACE
 ET11-04up GCTGTACTGGCTTTTCCTTCCCTCA (SEQ ID NO: 1589)
 ET11-04dn ACACCACCCCTGTGCTCACGTA (SEQ ID NO: 1590)
 ET11-05up CTGCTCTCAGACCTGGCCTACAT (SEQ ID NO: 1591)
 ET11-05dn CTAGGAAATGGTAAAGATGGCCTGG (SEQ ID NO: 1592)
 20 ET11-06up TGCCATGCTCCCATACCTGTACCTG; (SEQ ID NO: 1593) used in 3'
 RACE
 ET11-06dn CTCCACTGCTGTGGATCGTTGGCTT (SEQ ID NO: 1594)
 ET11-07up ATGTGGCCTCCTGGTCATTGTTAC (SEQ ID NO: 1595)
 ET11-07dn ATTTTGGCTTCTGTGTGTTGGTCAG (SEQ ID NO: 1596)
 25
 PGR6 cDNA sequence (SEQ ID NO: 91)
 ATGCAGCTGCACAGTTGCAGAGATGTGAATGCAGGAAGCCAGGTGTGAGTCTG
 AATTCACATTGGTTTTTTTATCTTTATTAAGCAGTCATTCCTAAGGCCTGCCCCGA
 GCCTGGCATCTCTACAGAGGAGTGGTGCCATCAGGACCCCTGTGGGGCAGATC
 30 AACACTCAAGGCAGGTGCAGAATCAACAACCTGTGACAAAGCCAGCCATCCCT
 GCCAGGAAGCATGGGGGATGAGCTGGCACCTTGCCCTGTGGGGCACTACAGCTT
 GGCCGGCCCTGATCCAGCTCATCAGCAAGACACCCTGCATGCCCCAAGCAGCC
 AGCAACACTTCCTTGGGCCTGGGGGACCTCAGGGTGCCCAGCTCCATGCTGTAC

TGGCTTTTCCTTCCCTCAAGCCTGCTGGCTGCAGCCACACTGGCTGTCAGCCCCC
 TGCTGCTGGTGACCATCCTGCGGAACCAACGGCTGCGACAGGAGCCCCACTACC
 TGCTCCCGGCTAACATCCTGCTCTCAGACCTGGCCTACATTCTCCTCCACATGCT
 CATCTCCTCCAGCAGCCTGGGTGGCTGGGAGCTGGGCCGCGATGGCCTGTGGCAT
 5 TCTCACTGATGCTGTCTTCGCCGCTGCACCAGCACCATCCTGTCTTACCCGCC
 ATTGTGCTGCACACCTACCTGGCAGTCATCCATCCACTGCGCTACCTCTCCTTCA
 TGTCCCATGGGGCTGCCTGGAAGGCAGTGGCCCTCATCTGGCTGGTGGCCTGCT
 GCTTCCCCACATTCTTATTTGGCTCAGCAAGTGGCAGGATGCCAGCTGGAGG
 AGCAAGGAGCTTCATACATCCTACCACCAAGCATGGGCACCCAGCCGGGATGT
 10 GGCCTCCTGGTCATTGTTACCTACACCTCCATTCTGTGCGTTCTGTTCTCTGCA
 CAGCTCTCATTGCCAACTGTTTCTGGAGGATCTATGCAGAGGCCAAGACTTCAG
 GCATCTGGGGGCAGGGCTATTCCCGGGCCAGGGGCACCCTGCTGATCCACTCAG
 TGCTGATCACATTGTACGTGAGCACAGGGGTGGTGTCTCCCTGGACATGGTGC
 TGACCAGGTACCACCACATTGACTCTGGGACTCACACATGGCTCCTGGCAGCTA
 15 ACAGTGAGGTACTCATGATGCTTCCCGTGCCATGCTCCCATACCTGTACCTGCT
 CCGCTACCGGCAGCTGTTGGGCATGGTCCGGGGCCACCTCCCATCCAGGAGGCA
 CCAGGCCATCTTTACCATTTCCTAGAGTCTTGAGTCCACAGTCTGGCAAGCTG
 AGGTAAAA

20 PGR6 polypeptide sequence (SEQ ID NO: 90)
 MGDELAPCPVGTTAWPALIQLISKTPCMPQAASNTSLGLGDLRVPSSMLYWLFPS
 SLLAAATLAVSPLLLVTILRNQRLRQEPHYLLPANILLSDLAYILLHMLISSSSLGGW
 ELGRMACGILTDAVFAACTSTILSFTAIVLHTYLAVIHPLRYLSFM SHGAAWKAVA
 LIWLVACCFTFLIWLSKWQDAQLEEQGYSLPPSMGTQPGCGLLVIVTYTSILCV
 25 LFLCTALIANCFWRIYAEAKTSGIWGQGYSRARGTLLIHSVLTLYVSTGVVFSLDM
 VLTRYHHIDSGHTWLLAANSEVLMMLPRAMLPYLYLLRYRQLLGMVRGHLPSR
 RHQAIFTIS

30 Human PGR10

Full length cDNA was isolated from human Pituitary by a combination of 5' and 3' Rapid
 Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as described
 above. RACE pituitary was prepared using the Clontech SMART RACE Kit (Cat # K1811-
 1).

35 The following CLONTECH RACE primers were used:

3'-RACE-CDS AAGCAGTGGTATCAACGCAGAGTACTTTTTTTTTTTTTTTTTT
 TTTTTTTTTTVN (SEQ ID NO: 1597)

40 5'-RACE-CDSTTTTTTTTTTTTTTTTTTTTTTTTTTVN (WHERE N=A,C,G,T AND

V=A,C,G) (SEQ ID NO: 1598)

Smart IIA AAGCAGTGGTATCAACGCAGAGTACGCGGG (SEQ ID NO: 1599)

NUP AAGCAGTGGTATCAACGCAGAGT (SEQ ID NO: 1600)

UPM-LONG CTAATACGACTCACTATAGGGCAAGCAGTGGTATCAACGCAGAGT

5 (SEQ ID NO: 1601)

UPM-SHORT CTAATACGACTCACTATAGGGC (SEQ ID NO: 1602)

The following cDNA primers were used:

J-H-PG63-U1 TGGATGATCTCATGAGCGTCCTG (SEQ ID NO: 1603)

10 J-H-PG63-L1 TCTGAAACCCACGACGTTCTG (SEQ ID NO: 1604)

J-H-PG63-U2 AGAACCGGGGACTCTCTATGG (SEQ ID NO: 1605)

J-H-PG63-L2 GGTGGGCAAAAAGAGGGAGTATG (SEQ ID NO: 1606)

J-H-PG63-U8 CACAAGTCAGATCTCCATCCCTACG (SEQ ID NO: 1607)

J-H-PG63-L8 TGCTGTATCCAGAAGCCTACCATGT (SEQ ID NO: 1608)

15 J-H-PG63-U7 GGACTGTGTCTCTCCATGCACCTAC (SEQ ID NO: 1609)

J-H-PG63-L7 GATCCATTCTTGCTCCTGTTAGACCA (SEQ ID NO: 1610)

J-H-PG63-U6 TGACTCTTATGCATGGGATTGATGA (SEQ ID NO: 1611)

J-H-PG63-L6 CTCCTACCAAGTTCCCCTCTAGATGTT (SEQ ID NO: 1612)

J-H-PG63-U5 AGATGGGATTCTGTGCACAAGCTC (SEQ ID NO: 1613)

20 J-H-PG63-L5 ACATGAAGATGGTCACCGACAGG (SEQ ID NO: 1614)

J-H-PG63-U3 GTAGAAATCAGCACCACGCCCTCT (SEQ ID NO: 1615)

J-H-PG63-U4 CAGATCTCCATCCCTACGTTACTCCA (SEQ ID NO: 1616)

PGR10 cDNA sequence determined by PCR and RACE (SEQ ID NO: 6)

25 TTTTTTTTTTATGCTTGAAATGGAACCTAATTTTTAAATATAGCTTGAGTCAGA
TCTAAAGGAGACATGGCTGACCATTTTCTGCAGGACTGACAAGGAGAACATCT
AGAGGGGAACTTGGTAGGAGGAATGAAATCTGATTTGCAGCAGCCGGTCTTTCT
TTTGAGAAAATTATCAGACTCATTGATAAGGGAAATTAATATTGACCAAGGAC
A[ATG]TCTTTATTTCTCAGTAACTTATCAACAAATGACTCTAGCCTGTGGAAAGA
30 GAATCATAATTCTACGGACCTTTTAAATCCGCCAGGAACCCTGAATATCTATCT
TTTTTGCTTGACATGTCTCATGACTTTTGCAGCCTTGGTGGGCAGCATTTATTCA
CTAATTTCCCTGCTGAAAATGCAGAACAGAACTGTTGTGTCCATGCTTGTGGCT
TCCTGGTCTGTGGATGATCTCATGAGCGTCCTGTCGGTGACCATCTTCATGTTTT

TGCAGTGGCCAAACGAGGTCCCCGGTTACTTCCAATTTCTGTGCACCACCTCTG
CCTTAATGTATTTATGCCAGGGCCTCTCTAGCAACTTGAAGGCGACTCTCCTAGT
CTCTTACAACCTTTTATACGATGCACAGAGGTGTGGGGAGCCAGACAGCCTCCAG
AAGATCGGGCCAGGTGCTCGGCGTGGTGTGACCGTGTGGGCAGCCAGTCTGCT
5 GCTCTCGGCGCTCCCGCTGTGCGGCTGGGGCGCCTTCGTGCGCACGCCCTGGGG
CTGCCTGGTGGACTGCTCCAGCTCCTACGTAATTCCTCTCTATCGTGTACGCT
TTGGCCTTCGGACTCCTCGTGGGCCTCTCAGTCCCACTCACTCACCGATTGCTGT
GTTCCGAGGAGCCGCCGAGACTCCACTCCAACCTACCAGGAAATTTCCCGTGGA
GCTTCAATTCCTGGGACCCCTCCTACTGCGGGGAGAGTGGTTTCCCTGTCCCCA
10 GAGGATGCTCCAGGCCCGAGTCTGCGGCGCTCTGGGGGATGCTCTCCGAGCTCC
GACACCGTGTTCGGACCGGGTGCGCCCGCTGCCGCTGGGGGCTGAAGCCTGCAG
GCGTGAGAACCAGGGGGACTCTCTATGGCACCAGGAGCTTCACCGTGAGCGTAG
CGCAGAAGCGCTTCGCTTTGATCCTAGCGCTTACAAAAGTCGTCCTTTGGCTGC
CCATGATGATGCACATGGTGGTCCAGAACGTCGTGGGGTTTCAGAGCCTTCCCT
15 TGGAGACATTCAGCTTTCTACTTACCCTGCTGGCCACCACTGTAACCCAGTGTT
TGTCTTGTCCAAACGCTGGACCCACTTGCCCTGTGGCTGCATCATCAACTGCAG
GCAGAACGCATATGCAGTGGCGTCCGATGGGAAAAAATCAAGAGAAAAGGCT
TTGAATTCAATCTATCATTCCAAAAAAGTTATGGGATTTATAAAATAGCACATG
AAGATTACTATGATGATGATGAAAATTCCATATTCTATCACAACCTGATGAACT
20 CTGAGTGTGAAACTACAAAAGACCCTCAGAGAGACAACCGTAACATCTTCAAT
GCTATAAAAGTAGAAATCAGCACCACGCCCTCTCTGGACAGCTCCACACAAAG
AGGCATCAACAAATGCACAAATACTGATATTACAGAAGCTAAACAGGATTCCA
ACAACAAAAAGGATGCGTTTTCTGACAAAACAGGAGGTGATATTAAGTATGAA
GAAACTACCTTTTTCTGAAGGGCCAGAAAGAAGACTGTCTCATGAAGAGAGTCA
25 GAAACCAGATCTTTCAGACTGGGAGTGGTGTAGGAGTAAATCAGAAAGAACCC
CTCGTCAGCGTTCGGGTTATGCCCTTGCCATTCCCTTGTGTGCATTCCAGGGGAC
TGTGTCTCTCCATGCACCTACAGGGAAAACCCCTATCTCTTTCTACCTATGAGGTA
AGCGCAGAAGGGGCAAAAAATAACTCCAGCCTCTAAGAAAATAGAAGTCTATCG
ATCCAAAAGTGTGGCCATGAACCAAACCTCAGAAGATTCTTCATCCACGTTTGT
30 GGACACCAGTGTGAAAATACACTTGGAGGTTCTTGAAATTTGTGATAATGAAGA
GGCCTTGGACACTGTGTCAATCATTAGTAACATCAGTCAGTCCTCCACACAAGT
CAGATCTCCATCCCTACGTTACTCCAGGAAAGAAAACAGATTTGTTTCATGTGA
CCTAGGGGAAACAGCCTCATACTCCCTCTTTTGGCCACCAGTAATCCTGATGG
TGATATTAATATCTCCATTCCAGACACAGTAGAAGCACACAGGCAGAACAGTA
35 AAAGGCAGCATCAAGAGAGGGATGGCTACCAGGAGGAAATCCAGTTGTAAAT
AAAGCTTACAGAAAAAGAGAGGAAGAAAGCAAGGGTAGTTAGTGGGTATTTG
GTCTAACAGGAGCAAGAATGGATCTGCAACGTCAACTGTGAAACTAACACCTTT
GTTATGAGACTGATTTCCCTTTTATTTGTTGGCTTACATTAGTTTTACTGATTTAAT
AGTTAATTTTTTTGTGGGAACAACCTGGAACCTAGTGTAACACTTAAGTGCATTT
40 GATGTGTTACCTAAAGATCACACACTGTGGTAATGAAAAGATTTTACTTCTTAT
CTGACTTCTAAAAAATATTTTCTAAATCAAATCTTGGCCTAGTTTACCAATGTTT
TTGCTTGTCAACTTCCTAGTAAACAGAAAAATTGTATAAACTCAGTGAATATACT
GTTCCATGCATATGTTTCTATATAAATGTTGGCCTTTACTGCAAAGGGGAAAA
AAGAGGAATTCTGGGAATGGAAGAAATGTAACAAAACCCCAAATTATATTT

PGR10 polypeptide sequence (SEQ ID NO: 5)

MSLFSLNLSTNDSSLWKENHNSTDLLNPPGTLNIYLFCLTCLMTFAALVGSISLISL
 LKMQRNRTVVSM LVASWSVDDLMSVLSVTIFMFLQWPNEVPGYFQFLCTTSALMY
 5 LCQGLSSNLKATLLVSYNFYTMHRGVGSQTASRRSGQVLGVVLTVWAASLLLSAL
 PLCGWGAFV RTPWGCLVDCSSSYVLFSLIVYALAFGLLVGLSVPLTHRLLCSEPPR
 LHSNYQEISRGASIPGTPPTAGR VVSLSPEDAPGPSLRRSGGCSPSSDTVFGPGAPAA
 AGAEACRREN RGTLYGTRSFTVSVAQKR FALILALT KVVLWLPMMM HMVVQNVV
 GFQSLPLETFSFLLTLLATT VTPVFVLSKR WTHLPCGCIINCRQ NAYAVASDGKKIK
 10 RKGFEFNLSFQKSYGIYKIAHEDYYDDDEN SIFYHNL MNSECETTKDPQRDN RNIFN
 AIKVEISTTPSLDSSTQRGINKCTNTDITEAKQDSNNKKDAFSDKTGGDINYEETFS
 EGPERRLSHEESQKPDLS DWEWCRSKSERTPRQRSGYALAIPLCAFQGT VSLHAPT
 GKTLSTLSTYEVSAEGQKITPASKKIEVYRSK SVGHEPNSEDSSSTFVDTSVKIHLEVL
 EICDNEEALDTVSIISNISQSSTQVRSPSLRYSRKENRFVSCDLGETASYSFLPTS NP
 15 DGDINISIPDTVEAHRQNSKRQH QERDGYQEEIQLLNKAYRKREEESKGS

Human PGR25

Full length cDNA was isolated from human Pituitary by a combination of 5' and 3' Rapid
 Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as described
 20 above. RACE pituitary was prepared using the Clontech SMART RACE Kit (Cat # K1811-
 1).

The following CLONTECH RACE primers were used:

3'-RACE-CDS AAGCAGTGGTATCAACGCAGAGTACTTTTTTTTTTTTTTTTTTTT
 25 TTTTTTTTTTVN (SEQ ID NO: 1597)
 5'-RACE-CDSTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTVN (WHERE N=A,C,G,T AND
 V=A,C,G) (SEQ ID NO: 1598)
 Smart IIA AAGCAGTGGTATCAACGCAGAGTACGCGGG (SEQ ID NO: 1599)
 NUP AAGCAGTGGTATCAACGCAGAGT (SEQ ID NO: 1600)
 30 UPM-LONG CTAATACGACTCACTATAGGGCAAGCAGTGGTATCAACGCAGAGT
 (SEQ ID NO: 1601)
 UPM-SHORT CTAATACGACTCACTATAGGGC (SEQ ID NO: 1602)

The following cDNA primers were used:

35 JW-H-PG208-L6 CGGTAATGGGAGGAATTCACGG (SEQ ID NO: 1617)

- JW-H-PG208-U2 CGGAGCAGACAGCCTTGAATCT (SEQ ID NO: 1618)
 JW-H-PG208-L2 GTGGATGTGGTAGCGCTGGTT (SEQ ID NO: 1619)
 JW-H-PG208-U3 AAATCCTGCCCAAGACCGTGAA (SEQ ID NO: 1620)
 JW-H-PG208-L3 CTGGCTCGAGGCGGAACTAA (SEQ ID NO: 1621)
 5 JW-H-PG208-U4 ACGGCTGTGCGCTCACGAGA (SEQ ID NO: 1622)
 JW-H-PG208-L4 AGCACGCCAAAGACCCACGAG (SEQ ID NO: 1623)
 J-H-PG208-U7 GCTGGAAAGGAGATCGCCATGT (SEQ ID NO: 1624)
 J-H-PG208-L7 TGGCCCATGACGGTGTCAATAG (SEQ ID NO: 1625)
 J-H-PG208-U8 GCGTGCTTGCTGTCAACGGTT (SEQ ID NO: 1626)
 10 J-H-PG208-L8 GCTCACACGGCTGACAGGTCG (SEQ ID NO: 1627)
 J-H-PG208-U9 TGTCTTCAACGCTGCCAAGCC (SEQ ID NO: 1628)
 J-H-PG208-L9 GGTACAGCAGACCCACGACGG (SEQ ID NO: 1629)
 J-H-PG208-U11 ATCCAAGGAGGGCCTGAAAGTCTA (SEQ ID NO: 1630)
 J-H-PG208-L11 CAAGGCTGTCTGCTCCGAGAG (SEQ ID NO: 1631)
 15 JW-H-PG208-U1 GCTGGAAAGGAGATCGCCATGT (SEQ ID NO: 1632)
 JW-H-PG208-L1 TGAAGTCCAGGAAGGCGCAGTA (SEQ ID NO: 1633)
 JW-H-PG208-U5 CCCCTGCCCTGTTTGTTCATCG (SEQ ID NO: 1634)
 JW-H-PG208-L5 GCTGTCTCGGGGCCACAACAC (SEQ ID NO: 1635)
 J-H-PG208-U10 TGACCTGGGAAAATCTATACGGTCG (SEQ ID NO: 1636)
 20 J-H-PG208-L10 TTGGTTATGATGGGATGGTAGGCA (SEQ ID NO: 1637)

PGR25 cDNA sequence (SEQ ID NO: 46)

- GGCCCCCTATTGGACTCATGTCCTATTTTACATGGAAATCCAAGGAGGGCCT
 GAAAGTCTACGTCAACGGGACCCTGAGCACCTCTGATCCGAGTGGA
 25 TGTCTCGTGACTATGGAGAGTCCAACGTCAACCTCGTGATAGGGTCTGAGC
 AGGACCAGGCCAAGTGTTATGAGAACGGTGCTTTCGATGAGTTCATCATCT
 GGGAGCGGGCTCTGACTCCGGATGAGATCGCCATGTACTTCACTGCTGCC
 ATTGGAAAGCATGCTTTATTGTCTTCAACGCTGCCAAGCCTCTTCATGACA
 TCCACAGCAAGCCCCGTGATGCCACAGATGCCTACCATCCCATCATAACC
 30 AACCTGACAGAAGAGAGAAAAACCTTCCAAAGTCCCGGAGTGATACTGAG
 TTACCTCCAAAATGTATCCCTCAGCTTACCCAGTAAGTCCCTCTCGGAGCA

GACAGCCTTGAATCTCACCAAGACCTTCTTAAAAGCCGTGGGAGAGATCC
 TTCTACTGCCTGGTTGGATTGCTCTGTCAGAGGACAGCGCCGTGGTACTGA
 GTCTCATCGACACTATTGACACCGTCATGGGCCATGTATCCTCCAACCTGC
 ACGGCAGCACGCCCCAGGTCACCGTGGAGGGCTCCTCTGCCATGGCAGAG
 5 TTTTCCGTGGCCAAAATCCTGCCCAAGACCGTGAATTCCTCCCATTACCGC
 TTCCCGGCCACGGGCAGAGCTTCATCCAGATCCCCACGAGGCCTTCCAC
 AGGCACGCCTGGAGCACCGTCGTGGGTCTGCTGTACCACAGCATGCACTA
 CTACCTGAACAACATCTGGCCCGCCCACACCAAGATCGCGGAGGCCATGC
 ATCACCAGGACTGCCTGCTGTTGCGCCACCAGCCACCTGATTTCCCTGGAGG
 10 TGTCCCCACCACCCACCTGTCTCAGAACCTGTCGGGCTCTCCACTCATT
 CGGTCCACCTCAAGCACAGATTGACACGTAAGCAGCACAGTGAGGCCACC
 AACAGCAGCAACCGAGTCTTCGTGTACTGCGCCTTCCTGGACTTCAGCTCC
 GGAGAAGGGGTCTGGTTCGAACCACGGCTGTGCGCTCACGAGAGGAAACCT
 CACCTACTCCGTCTGCCGCTGCACTCACCTACCAACTTTGCCATCCTCAT
 15 GCAGGTGGTCCCGCTGGAGCTTGACGCGGACACCAGGTGGCGCTGTCGT
 CTATCAGCTATGTGGGCTGCTCCCTCTCCGTGCTCTGCCTGGTGGCCACGC
 TGGTCACCTTCGCCGTGCTGTCCTCCGTGAGCACCATCCGGAACCAGCGCT
 ACCACATCCACGCCAACCTGTCCTTCGCCGTGCTGGTGGCCCAGGTCTGCT
 TGCTCATTAGTTTCCGCCTCGAGCCaGGCACGACCCCCTGCCAAGTGATGG
 20 CCGTGCTCCTACACTACTTCTTCCTGAGTGCCTTCGCATGGATGCTGGTGG
 AGGGGCTGCACCTCTACAGCATGGTGATCAAGGTCTTTGGGTCCGAGGAC
 AGCAAGCACCGTTACTACTATGGGATGGGATGGGGTTTTCTCTTCTGATC
 TGCATCATTTCACTGTCAATTTGCCATGGACAGTTACGGAACAAGCAACAAT
 TGCTGGCTGTGCTTGGCGAGTGGCGCCATCTGGGCCTTTGTAGCCCCTGCC
 25 CTGTTTGTATCGTGGTCAACATTGGCATCCTCATCGCTGTGACCAGAGTC
 ATCTCACAGATCAGCGCCGACAACTACAAGATCCATGGAGACCCCAAGTGC
 CTTCAAGTTGACGGCCAAGGCAGTGGCCGTGCTGCTGCCCATCCTGGGTAC
 CTCGTGGGTCTTTGGCGTGCTTGTGCTGCAACGGTTGTGCTGTGGTTTTCCAG
 TACATGTTTGCCACGCTCAACTCCCTGCAGGGACTGTTCAATTCCTCTTTC
 30 ATTGTCTCCTGAATTCAGAGGTGAGAGCCGCCTTCAAGCACAAAATCAAG
 GTCTGGTCGCTCACGAGCAGCTCCGCCCGCACCTCCAACGCGAAGCCCTTC
 CACTCGGACCTCATGAATGGGACCCGGCCAGGCATGGCCTCCACCAAGCT
 CAGCCCTTGGGACAAGAGCAGCCACTCTGCCACCGCGTCGACCTGTCAG
 CCGTGTGAGC

35

PGR25 polypeptide sequence (SEQ ID NO: 45)

MSYFTWKSKEGLKVYVNGTLSTSDPSGKVS RDYGESNVNLVIGSEQDQAKC
 YENGAFDEFIWERALTPDEIAMYFTAAIGKHALLSSTLPSLFMTSTASPMPT
 DAYHPIITNLTEERKTFQSPGVILSYLQNVSLSLPSKSLSEQTALNLTKTFLKAV
 40 GEILLPGWIALSEDSAVVLSLIDTIDTVMGHVSSNLHGSTPQVTVEGSSAMAE
 FSVAKILPKTVNSSHYRFPAGHQSFQIPHEAFHRHAWSTVVGLLYHSMHYLY
 NNIWPAHTKIAEAMHHQDCLLFATSHLISLEVSPPTLSQNLSGSPPLITVHLKH
 RLTRKQHSEATNSSNRV FVYCAFLDFSSGEGVWSNHGCALTRGNLTYSVCRC
 THLTNFAILMQVVPLELARGHQVALSSISYVGCSLSVLCLVATLVTFVLSSVS

TIRNQRVYHIHANLSFAVLVAQVLLISFRLEPGTTPCQVMAVLLHYFFLSAFA
 WMLVEGLHLYSMVIKVFGESESKHRYYYGMGWGFPLLCIISLSFAMDSYGT
 SNNCWLSLASGAIWAFVAPALFVIVVNIGILIAVTRVISQISADNYKIHGDPSAF
 5 KLTAKAVAVLLPILGTSWVFGVLA VNGCAVVFQYMFATLNSLQGLFIFL FHC
 LLNSEVRAAFKHKIKVWSLTSSSARTSNAKPFHSDLMNGTRPGMASTKLSPW
 DKSSHSAHRVDLSAV

Human PGR17

10 Full length cDNA was isolated from human Pituitary by a combination of 5' and 3'
 Rapid Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as
 described above. RACE pituitary was prepared using the Clontech SMART RACE Kit (Cat
 # K1811-1).

15 The following CLONTECH RACE primers were used:

3'-RACE-CDS AAGCAGTGGTATCAACGCAGAGTACTTTTTTTTTTTTTTTTTTTT
 TTTTTTTTTTVN (SEQ ID NO: 1597)

5'-RACE-CDSTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTVN (WHERE N=A,C,G,T AND
 V=A,C,G) (SEQ ID NO: 1598)

20 Smart IIA AAGCAGTGGTATCAACGCAGAGTACGCGGG (SEQ ID NO: 1599)

NUP AAGCAGTGGTATCAACGCAGAGT (SEQ ID NO: 1600)

UPM-LONG CTAATACGACTCACTATAGGGCAAGCAGTGGTATCAACGCAGAGT
 (SEQ ID NO: 1601)

UPM-SHORT CTAATACGACTCACTATAGGGC (SEQ ID NO: 1602)

25

The following cDNA primers were used:

J-H-PG421-U1 CCTGGGCAGAGAAGACATAGACCT (SEQ ID NO: 1638)

J-H-PG421-L1 GTAATTTGGGATGGAGTGGTCATATCT (SEQ ID NO: 1639)

J-H-PG421-U2 GGCTTCATTTCATATGGCATAACAAT (SEQ ID NO: 1640)

30 J-H-PG421-L2 TCAATAAGCCTAGTTGGGAGAGTCAAT (SEQ ID NO: 1641)

J-H-PG421-U3 AGCTGCCGGAAGTGTACCTTGGTTTAC (SEQ ID NO: 1642)

J-H-PG421-L3 AGCCACCACAGAACTGCCATTAAGT (SEQ ID NO: 1643)

J-H-PG421-U4 GAGCACACATATATTCGGTGAACCC (SEQ ID NO: 1644)

| | | |
|----|---------------|--|
| | J-H-PG421-L4 | CTGGCAATGAGGACATCTGGTAAA (SEQ ID NO: 1645) |
| | J-H-PG421-U5 | AGTCACCAAACACATTCGCCTTC (SEQ ID NO: 1646) |
| | J-H-PG421-L5 | CCCAGATAATATGCCCAAAGTTGTAGC (SEQ ID NO: 1647) |
| | J-H-PG421-U6 | TGGGCATATTATCTGGGATTACTAACA (SEQ ID NO: 1648) |
| 5 | J-H-PG421-L6 | CAGCCAATGTGGAAGTGATAGC (SEQ ID NO: 1649) |
| | J-H-PG421-U7 | TGGCAATGTCATCAATTCCTATGTCAG (SEQ ID NO: 1650) |
| | J-H-PG421-L7 | GTTTGGGCTGTCTCCGTAGGGTT (SEQ ID NO: 1651) |
| | J-H-PG421-U8 | CCTTTCTATCTACGGAAGCATCGACTT (SEQ ID NO: 1652) |
| | J-H-PG421-L8 | GGCACTCACAACATAGGTGGTTAATG (SEQ ID NO: 1653) |
| 10 | J-H-PG421-U9 | GTGAGTGCCAGCATTTTCAGATGATATG (SEQ ID NO: 1654) |
| | J-H-PG421-L9 | TGACTGTGATTGCCACCATGATAGC (SEQ ID NO: 1655) |
| | J-H-PG421-U10 | TGCCAAAACAAAAATCACATGCTAATG (SEQ ID NO: 1656) |
| | J-H-PG421-L10 | CAGGTTGTGTGGTTGATCCGTTACTT (SEQ ID NO: 1657) |
| | J-H-PG421-U11 | CTATCATGGTGGCAATCACAGTCAGT (SEQ ID NO: 1658) |
| 15 | J-H-PG421-L11 | GTGAGTCAACCCTACAAATCCGAAAAA (SEQ ID NO: 1659) |

PGR17 cDNA sequence (SEQ ID NO: 30)

| | |
|----|---|
| | TTCTTCTTTCATTTACATCAAACATAGGAATTTAGAGACAAGATCTGGTCATTT |
| | GAGGGTGGGAAGTTAAAAGAGTCCAGTTCTCAGACTTAGACAATGAAAGAACA |
| 20 | CATCATATATCAGAAGCTTTATGGATTGATTCTCATGTCGAGTTTATCTTTCTC |
| | TCAGATACACTTTCACTAAAAGGAAAAAAGCTGGATTTTTTTTGGAAAGAGGTGAC |
| | ACATATGTAAGCCTGATAGATACCATTCTGAAGTCAAGCTGAGCCGATTCACAGCATGC |
| | ATTGATCTGGTATTCATGGATGACAACCTCAAGGTATTGGATGGCCTTCTCTTATA |
| | TTACTAATAACGCCCTCCTGGGCAGAGAAGACATAGACCTTGGACTTGCAGGA |
| 25 | GACCATCAGCAGCTAATACTATACAGATTGGGAAAGACCTTTTCTATCCGTCAC |
| | CACCTGGCTTCATTTCAATGGCATAACAATATGCTTGATATGGGATGGTGTGAAG |
| | GGCAAATTAGAACTCTTCTGAATAAAGAAAGGATACTGGAAGTAACGGATCA |
| | ACCACACAACCTGACACCTCATGGGACTCTGTTCTAGGGCACTTTCTCAAGAA |
| | TGAGAGCAGCGAGGTTAAAAGCATGATGCGTAGCTTCTGAGCAGCTTGTA |
| 30 | CTTTCAACTCTGGGACCACATCCTGGAAAACGAAGAGTTTATGAAGTGTTTGA |
| | TGGAAATATAGTTAGTTGGGAAGAAGACGTCTGGCTTGTCACCAAGATCATCCC |
| | AACTGTTGACAGGACACTGCGCTGCGTTCTGAAAATATGACAATTCAAGAAA |
| | AAAGTACAACCTGTTTCACAACAGATAGATATGACCACTCCATCCCAAATTACTG |
| | GAGTAAAACCACAAAATACTGCACATTCCTCTACACTATTGTCTCAAAGCATAC |
| 35 | CTATATTTGCAACTGATTACACAACCATATCATATTCCAATACAACATCTCCACC |
| | TCTGGAAACAATGACTGCACAAAAAATCTTAAAGACACTGGTAGATGAGACAG |

CTACATTTGCAGTGGATGTTTTATCAACTTCATCAGCCATCTCTCTGCCTACCCA
GAGTATATCCATAGACAATACTACCAATTCCATGAAAAAACGAAATCTCCATC
TTCAGAAAGCACAAAGACAACAAAAATGGTTGAAGCCATGGCTACTGAAATCT
TTCAACCACCTACACCTTCTAATTTCTATCCACATCCAGATTTACCAAGAATTC
5 AGTTGTATCTACAACTTCAGCAATTAATCTCAGTCGGCTGTTACGAAGACAAC
ATCTTTATTTTCAACTATTGAGTCAACATCTATGTCTACAACACCTTGTCTCAA
CAAAAATCCACAAATACTGGGGCACTCCCTATCTCCACAGCTGGCCAGGAGTTC
ATTGAATCTACAGCTGCCGGAACGTACCTTGGTTTACAGTGGAAAAGACTTCA
CCTGCATCTACTCATGTTGGGACTGCATCATCAATCCCACCTGAGCCTGTGCTCA
10 TCTCCACAGCTGCTCCAGTAGATTCTGTATTTCCCTAGAAACCAGACAGCATTTCC
ATTGGCAACAACCTGATATGAAAATAGCATTTACAGTCCATTCAATTGACTCTCCC
AACTAGGCTTATTGAGACCACACCTGCCCCAAGGACAGCTGAAACAGAATTGA
CATCTACAAATTTTTCAGGATGTCTCTTTACCCAGAGTGGAAAGATGCCATGTCTA
CTTCCATGTGCAAAGAGACCTCCTCTAAGACCTTTTCTTTCTTAACATCCTTTTC
15 ATTTACTGGGACTGAGAGTGTACAGACAGTTATTGATGCTGAAGCTACACGTAC
AGCCTTAACTCCTGAAATCACACTTGCATCTACAGTGGCTGAAACTATGCTTTC
CTCCACAATCACAGGACGAGTTTACACCCAGAATACACCTACAGCTGATGGAC
ACTTGCTTACTTTGATGTCCACTAGATCAGCTTCCACATCCAAGGCACCTGAGTC
AGGTCACATCCACAACCTGATGAAGCTGCCCATCTGTTCTCCAGCAATGAGAC
20 CATTTGGACTTCTAGGCCAGACCAGGCCCTGCTGGCATCTATGAACACAACCAC
CATACTCACATTTGTGCCTAATGAAAATTTTACATCAGCATTTTCATGAGAATACT
ACTTATACAGAATATTTATCCGCAACTACCAATATCACCCCACTGAAAGCATCT
CCAGAGGGCAAAGGTACCACTGCCAATGATGCTACTACAGCCAGATATACAAC
AGCTGTATCCAAATTGACATCACCATGGTTTGCTAATTTCTCCATAGTTTCTGGA
25 ACCACATCCATAACCAATATGCCTGAATTTAACTTACCACTTTACTACTAAAA
ACAATACCTATGTCTACAAAACCTGCAAATGAACTTCCTTTGACACCAAGGGAG
ACTGTTGTTCCATCAGTAGATATAATATCTACTCTTGCTTGCATTCAACCAAATT
TTTCTACTGAGGAAAGTGCTTCTGAGACCACACAAACAGAAATAAATGGTGCA
ATTGTATTTGGAGGTACAACGACCCCTGTACCAAAGTCAGCAACAACACAAAG
30 ATTAAATGCCACTGTGACAAGAAAAGAAGCAACTTCCCATTTTCAACAATGCTGGAAGT
ATCAACTATAGCAGCAGTGGCTGAGGTTTCTCCATTTTCAACAATGCTGGAAGT
GACAGACGAATCAGCACAAAGGGTGACAGCTTCTGTCACTGTTTCTCTTTTCC
TGATATAGAAAAGCTAAGTACCCCATTTGGATAATAAACTGCAACAACCTGAGG
TGAGAGAAAGTTGGCTTTTGACAAAATTGGTGAAAACCACACCTAGGAGTTCAT
35 ACAATGAAATGACAGAAATGTTTAATTTTAAACCACACCTATGTAGCACATTGGA
CTTCAGAGACATCTGAGGGAATTTAGCTGGATCTCCCACTTCTGGGAGCACAC
ATATATTCGGTGAACCCCTGGGTGCTTCTACCACAAGGATATCAGAAACCAGTT
TCTCCACTACCCCTACAGACAGGACAGCTACGTCCTTGTCTGATGGTATCTTACC
TCCACAGCCTACAGCTGCTCATTCTCAGCAACCCCTGTGCCTGTTACTCATATG
40 TTCTCATTGCCAGTTAATGGCAGTTCTGTGGTGGCTGAGGAGACTGAGGTTACC
ATGTCTGAGCCTTCTACACTGGCCAGGGCTTTTTCTACATCTGTGCTCTCAGATG
TCTCAAATCTATCCTCAACTACAATGACCACAGCATTGGTACCACCTTTGGATC
AGACTGCTTCCACAACCATTGTTATTGTGCCTACCCATGGAGACTTGATTCGTAC
CACTTCAGAGGCCACGGTAATCTCTGTGAGGAAGACATCCATGGCAGTTCCTTC

TCTGACAGAAACACCATTTTCATTCACTGAGACTCTCCACTCCTGTGACAGCTAA
GGCTGAGACCACCCTTTTCTCTACCTCAGTTGATACAGTAACCCCATCTACACA
CACTCTTGTCTGCTCAAAACCTCCCCCTGACAACATTCTCCTGCGTCTCCACT
CATGTGATCTCAACTACGTCTACACCAGAAGCAACTCAACCAATATCTCAAGTA
5 GAGGAGACTTCTACCTATGCTCTCAGCTTCCCATATACITTTTCAGTGGTGGTGGG
GTTGTTGCCAGCTTGGCTACTGGCACCACAGAGACCTCTGTTGTTGATGAGACC
ACACCTCACAATCTCTGCCAATAAGTTGACTACTTCAGTAAACAGTCAATT
TCTTCATCTGCCACATATCGTGTACACACACCAGTGTCCATCCAGTTGGTGA
10 GCACCTCTGTCTTATCTTCCGACAAAGACCAGATGACCATATCCCTGGGAAAAA
CATACTCCCGGGGTACTCCATCTTTGGAAATGACAGATACAGGATTTCTGAGA
CCACAAAAATTTCCAGTCACCAAACACATTTCGCCTTCAGAGATTCCACTTGGGA
CTCCCTCTGATGGAAATTTGGCTTCATCTCCCACTTCTGGAAGCACACAGATTAC
ACCAACCTTGACCTCAAGTAACACAGTAGGTGTTTACATTCCAGAAATGTCTAC
15 CAGTCTTGGGAAAACAGCTCTCCCTCACAAGCTCTGACAATCACCCTTTTT
GTGCTCTGAAAAGGAAAGCACGAGTGCCCTTCCAGCATATACTCCAGGACTGT
GGAAATGATAGTAACTCCACCTATGTGACTCACTCTGTCTCATATGGCCAGGA
TACTTCATTTGTAGATACCACAACCTTCAGCTCAACAAGGATATCAAATCCTAT
GGACATCAATACAACCTTTTTTACACTTGCATTCACTTAGGACACAACCTGAGGT
20 GACTTCAGTTGCCTCTTTTCACTTCTGAAAGCACACAGACTTTCCCTGAGTCCTTG
TCTCTTTCCACAGCTGGACTATATAATGACGGTTTTACAGTTCTCTCCGACAGGA
TCACTACAGCCTTTTCTGTTCCAAATGTACCTACAATGCTTCCTAGAGAATCCTC
TATGGCAACGTCCACTCCTATTTACCAGATGTCTCATTGCCAGTTAATGTAAC
GCCTTCACCTCCAAAAAAGTTTCTGACACTCCCCCAATAGTGATAACTAAATCT
25 TCTAAAACAATGCATCCAGGTTGTTTGAAAAGTCCCTGTACAGCCACTTCTGGG
CCTATGTCTGAGATGTCTCAATAACAGTTAATAACTCTGCTTTCACACCTGCAA
CAGTCTCTTCTGACACTTCCACAAGAGTTGGGTTATTCTCTACTTTATTGTCTTC
AGTTACCCCCAGGACTACTATGACCATGCAAACATCTACATTGGATGTACACAC
TGTGATATATGCTGGGGCTACTTCAAAAAACAAAATGGTTTCCTCTGCTTTCCT
30 ACAGAAATGATAGAGGCACCTTCCAGGATCACACCTACGACCTTTCTCTCTCCA
ACAGAGCCAACCTTTGCCCTTTGTAAAAACCGTTCCCACCACCATATGGCTGGG
ATAGTGACTCCATTTGTAGGCACCACTGCCTTCTCTCCACTCAGTTCTAAGAGCA
CTGGAGCTATTTCTCCATTCCAAAGACCACATTTTACCATTCTATCAGCAAC
TCAACAGTCATCACAAGCAGATGAGGCTACAACCTTTGGGCATATTATCTGGGAT
35 TACTAACAGGTCCCTATCTACTGTGAACAGTGGTACAGGGGTAGCTCTCACAGA
TACTTATTCCAGAATCACTGTTCCCTGAAAATATGCTTTCACCTACTCATGCAGAT
AGTCTCCATACTTCTTCAATATTCAGGTTTCCCCATCTCTGACTAGCTTTAAGA
GTGCTTCTGGACCCACAAAAAATGTTAAAAACAACCAATTGCTTTTCTTCTA
ATACTAGAAAGATGACTTCCTTGTTAGAAAAGACTTCCTTAACAACTATGCCA
40 CATCTTTGAATACCCCTGTTTCATACCCCTCCATGGACCCCATCCAGTGCAACTCT
ACCTCTTTGACATCATTTGTTTATTACCTCATAGTACTGAAGCTGAGATCTCT
ACTCCAAAGACCTCTCCTCCTCCCATCCCAATGGTTGAATTTCCAGTTCTGG
GAACAAGAATGACATCTAGTAATACCCAACCTCTGCTTATGACTTCCTGGAACA
TACCCACAGCTGAAGGTTCTCAGTTTCCAATTTCCACCCTATTAATGTACCTAC

ATCCAATGAGATGGAAACAGAGACTCTACACCTTGTTCTGGGCCTTTGTCAAC
ATTCACAGCCTCTCAGACTGGTCTAGTATCTAAAGATGTCATGGCAATGTCATC
AATTCCTATGTCAGGAATTCTTCCTAACCATGGGCTTTCTGAGAACCCTTCATTA
TCAACATCTTTAAGAGCTATCACTTCCACATTGGCTGACGTTAAGCACACATTT
5 GAGAAAATGACCACATCTGTAACCTCTGGGACCACACTCCCATCAATTCTTTCT
GGTGCCACTTCAGGATCTGTAATTTCAAAGTCACCCATTCTGACATGGCTCTTAT
CTAGTCTCCCTTCTGGCTCCCTCCGGCAACTGTATCTAATGCCCTCATGTTAT
GACTTCCTCTACAGTAGAGGTGTCAAAATCAACATTTCTGACATCTGACATGAT
ATCAGCGCACCCATTCACTAACTTGACAACACTACCCTCTGCTACTATGAGCAC
10 CATACTCACCCGAACCATTCTACACCTACACTGGGTGGTATCACTACTGGCTT
CCCAACTTCTCTCCCTATGTCTATAAATGTCACAGATGACATTGTGTACATTTCC
ACACACCTGAGGCATCCTCCAGAACCACAATAACTGCCAACCCAGGACTGT
GTCTCATCCTTCATCCTTCAGCAGAAAGACTATGTCACCTTCTACAACCTGACCAC
ACTCTATCTGTTGGTGCCATGCCTCTGCCTAGCTCTACAATAACATCTTCATGGA
15 ACAGAATTCCAACCTGCATCATCACCTCTACTTTAATTATTCCTAAGCCCACACT
GGACTCCCTTCTAAATATAATGACTACTACATCCACTGTTCTGGAGCCTCATTT
CCACTCATATCCACTGGGGTGACATATCCTTTTACAGCAACTGTGTCTTCACCAA
TATCGTCCTTTTTTGAACAACCTGGCTGGACTCCACACCTTCCTTTCTATCTAC
GGAAGCATCGACTTCGCCTACTGCCACCAAGTCCACAGTTTCCTTCTACAATGT
20 TGAAATGAGCTTCTCTGTCTTTGTTGAAGAGCCAAGGATCCCTATTACCAGTGTT
ATAAATGAATTTACGGAAAATTCGTTGAATTCTATATTTCAGAACAGTGAATTT
TCTCTTGCTACTCTGGAAACCCAAATTAAGCAGGGACATTTACAGAGGAAGA
GATGGTCATGGATCGAGCTATTTTGAACAGAGAGAAGGACAAGAAATGGCTA
CAATTTCTATGTACCATACAGTTGTGTTTGTGAGGTCATCATAAAGCCAGCTC
25 TTCTTAGCATCCTCTGAATTGATGAGAAAAATCAAAAGTAAAATACATGGCAA
CTTCACACATGGAACTTCACACAAGATCAATTGACGTTATTAGTAAACTGTGA
ACACGTTGCAGTGAAAAAACTAGAGCCTGGAAATTGCAAAGCTGATGAAACAG
CCTCTAAATACAAAGGGACCTATAAGTGGCTATTAACCAACCCTACGGAGACA
GCCCAAACCAGATGCATAAAAAATGAGGATGGAAATGCCACAAGATTCTCAAT
30 CAGCATCAACACGGGCAAATCTCAGTGGGAAAAGCCAAAGTTTAAACAATGCA
AATTGCTTCAAGAACTTCCTGACAAGATTGTGGATCTTGCTAATATTACCATAA
GTGATGATTTTCTAGGCAATGTCCCTGTGGGAGGGATTTTGGCTTCCATATATT
TGCTTAAATCACTGACGGAGAGAATTCCTCTTAGCAACTTACAAACGATCTTGT
TTAATTTCTTTGGCCAACTTCACTCTTTAAGACCAAAAATGTCACTAAAGCATT
35 AACCACCTATGTTGTGAGTGCCAGCATTTCAGATGATATGTTCAATCAAACTT
AGCTGACCCAGTGGTTATCACTCTGCAGCATATTGGAGGAAACCAGAATTATGG
TCAAGTTCAGTGTGCCTTTTGGGATTTTGAAGAATAATGGGCTGGGTGGATGGAA
TTCGTCAGGCTGTAAAGTAAAGGAAACAAATGTAAATTACACAATCTGTCAGTG
TGACCACCTCACCCATTTTGGAGTCTTAATGGAACTTCGAAAAGATTATCCTG
40 CCAAAATTCTGATCAACCTGTGCACAGCACTACTGATGCTAAACCTGGTATTTT
TGATCAATTCTTGGTTGTTCATCATTTTCAGAAAGTGGGAGTTTGTATCACAGCTGC
AGTGGCACTTCATTACTTCCTGCTTGTCTTTTACTTGGATGGGCCTGGAGGCA
GTCCACATGTATTTGGCTCTAGTCAAAGTCTTCAACATATACATTCCAAATTATA
TCCTTAAATTTTGTCTAGTTGGTTGGGGAATCCCGGCTATCATGGTGGCAATCAC

AGTCA

PGR17 polypeptide sequence (SEQ ID NO: 29)

5 MKEHIYQKLYGLILMSSFIFLSDTLSLKGKKLDFGRGDTYVSLIDTIPELSRFTACI
 DLVFMDDNSRYWMAFSYITNNALLGREDIDLGLAGDHQQLILYRLGKTFSIRHHLA
 SFQWHTICLIWDGVKGKLELFLNKERILEVTDQPHNLTPHGTFLGLHFLKNESSEVK
 SMMRSFPGSLYYFQLWDHILENEEFMKCLDGNIVSWEEDVWLVNKIPTVDRTLRC
 10 VPENMTIQEKSTTVSQIDMTTPSQITGVKPQNTAHSSTLLSQSIPIFATDYTTISYSN
 TTSPPLETMTAQKILKTLVDETATFAVDVLSTSSAISLPTQSIIDNTTNSMKKTKSPS
 SESTKTTKMVEAMATEIFQPPTPSNFLSTSRFTKNSVVSTTSAIKSQSAVTKTTSLFST
 IESTSMSTTPCLKQKSTNTGALPISTAGQEFIESTAAGTVPWFTVEKTSPASTHVGT
 SSFPPEPVLISTAAPVDSVFPRNQTAFLATTDMKIAFTVHSLTLPTRLIETTPAPRTA
 ETELTSTNFQDVS LPRVEDAMSTSMKETSSKTF SFLTSFSFTGTESVQTVIDAEATR
 15 TALTPETLASTVAETMLSSTITGRVYTQNTPTADGHLLTLMSTRSASTSKAPESGPT
 STTDEAAHLFSSNETIWT SRPDQALLASMNTTITLTFVPNENFTSAFHENTTYTEYLS
 ATTNITPLKASPEGKGTANDATTARYTTAVSKLTSPWFANFSIVSGTTSITNMPEFK
 LTLLLLKTIPMSTKPANELPLTPRETVPVPSVDIISTLACIQPNFSTEEASSETTQTEING
 AIVFGGTTTPVPKSATTQRLNATVTRKEATSHYLMRKSTIAAAVAEVSPFSTMLEVD
 20 ESAQRVTASVTVSSFPDIEKLSTPLDNKTATTEVRESWLLTKLVKTTPRSSYNEMTE
 MFNFNHTYVAHWTSSETSEGISAGSPTSGSTHIFGEPLGASTTRISETSFSTTPTDRTAT
 SLSDGILPPQPTAAHSSATPVVTHMFSLPVNGSSVVAEETEVTMSEPSTLARAFSTS
 VLSDVSNLSSTTMTALVPPLDQASTTIVIVPTHGDLIRTTSEATVISVRKTSMAVP
 SLTETPFHSLRLSTPVTAKAETTLFSTSVDTVTPSTHTLVCSKPPPDNIPPASSTHVIST
 25 TSTPEATQPISQVEETSTYALSFPYTFSGGGVVASLATGTTETSVVDETTPSHISANK
 LTTSVNSHISSSATYRVHTPVSIIQLVTSTSVLSSDKDQMTISLGKTPRTMEVTEMSPS
 KNSFISYSRGTPSLEMTDTGFPETTKISSHQTHSPSEIPLGTPSDGNLASSPTSGSTQIT
 PTLTSSNTVGVIPEMSTSLGKTALPSQALTITFLCPEKESTSALPAYTPRTVEMIVN
 STYVTHSVSYGQDTSFVDTTTSSSTRISNPM DINTTFSHLHSLRTQPEVTSVASFISES
 30 TQTFPESLSLSTAGLYNDGFTVLSDRITTAFSVPNVPTMLPRESSMATSTPIYQMSSL
 PVNVTAFTSKKVSDTPPIVITKSSKTMHPGCLKSPCTATSGPMSEMSSIPVNNSAFTP
 ATVSSDTSTRVGLFSTLLSSVTPRTTMTMQTSTLDVTPVIYAGATSKNKMVSSAFTT
 EMIEAPSRITPTTFLSPTEPTLPFVKTVPTTIMAGIVTPFVGTTAFSPLSSKSTGAISSIP
 KTTFSPLSATQQSSQADEATTLGILSGITNRSLSLVNSGTGVALTDYSRITVPENM
 35 LSPTHADSLHTSFNIQVSPSLTSFKSASGPTKNVKTNTNCFSSNTRKMTSLLEKTSLT
 NYATSLNTPVSYPPWTPSSATLPSLTSFVYSPHSTEA EISTPKTSPPTSQMVEFPVLG
 TRMTSSNTQPLLMTSWNIPTAEGSQFISTTINVPTS NEMETETLHLVPGPLSTFTAS
 QTGLVSKDVMAMSSIPMSGILPNHGLSENPSLSTSLRAITSTLADV KHTFEKMTTSV
 TPGTTLPSILSGATSGSVISKSPILTWLSSLP SGSPPATVSNAPHVMTSSTVEVSKSTF
 40 LTSDMISAHPTNLTLPSATMSTILTRTIPTPLGGITGFTSLPMSINVTDDIVYIST
 HPEASSRTTITANPRTVSHPSFSRKTMSPSTTDHTLSVGAMPLPSSTITSSWNRIPTA
 SSPSTLIIPKPTLDSLLNIMTTTSTVPGASFPLISTGV TYPFTATVSSPISSFFETT WLD
 TPSFLSTEASTSPTATKSTVSFYNVEMSFVFE EPRIPITSVINEFTENSLNSIFQNSEF
 SLATLETQIKSRDISEEEMVMDRAILEQREGQEMATISYVPYSCVCQVIKASSSLAS

SELMRKIKSKIHGNTFHGNFTQDQLTLLVNCEHVA VKKLEPGNCKADETASKYKG
 TYKWLLTNPTETAQTRCIKNEDGNATRFSSISINTGKSQWEKPKFKQCKLLQELPDKI
 VDLANITISDDFPRQCPCGRDFGFHIFA

5 Human KIAA1828

Full length cDNA was isolated from human Pituitary by a combination of 5' and 3' Rapid Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as described above. RACE pituitary was prepared using the Clontech SMART RACE Kit (Cat # K1811-1). Pituitary poly A RNA was obtained from Clontech (cat# 6584-1).

10

The following CLONTECH RACE primers were used:

3'-RACE-CDS AAGCAGTGGTATCAACGCAGAGTACTTTTTTTTTTTTTTTTTTTT
 TTTTTTTTTTVN (SEQ ID NO: 1597)

5'-RACE-CDSTTTTTTTTTTTTTTTTTTTTTTTTTTVN (WHERE N=A,C,G,T AND

15

V=A,C,G) (SEQ ID NO: 1598)

Smart IIA AAGCAGTGGTATCAACGCAGAGTACGCGGG (SEQ ID NO: 1599)

NUP AAGCAGTGGTATCAACGCAGAGT (SEQ ID NO: 1600)

UPM-LONG CTAATACGACTCACTATAGGGCAAGCAGTGGTATCAACGCAGAGT
 (SEQ ID NO: 1601)

20

UPM-SHORT CTAATACGACTCACTATAGGGC (SEQ ID NO: 1602)

The following cDNA primers were used:

J-H-1828-U1 AGCCCCGCAATCTGTTGATAACT (SEQ ID NO: 1660)

J-H-1828-L1 AAGCAGAAATTCAGGAGCGTGTG (SEQ ID NO: 1661)

25

J-H-1828-U2 TGGAGAAGGAGACGCATCTGC (SEQ ID NO: 1662)

J-H-1828-L2 CTTGGTCACCTGCTTGTAGATGTT (SEQ ID NO: 1663)

J-H-1828-U3 CCTGACCTTTCCAGTGTTCAATGT (SEQ ID NO: 1664)

J-H-1828-L4 TTGTCCATGAGAATCTCCCGTCTG (SEQ ID NO: 1665)

J-H-1828-U5 GGACCCTGGAAAAACGAACTACTG (SEQ ID NO: 1666)

30

J-H-1828-L5 TCCATGAGAATCTCCCGTCTGTC (SEQ ID NO: 1667)

J-H-1828-U6 TGTGTACTTCCTGGGCACCTACG (SEQ ID NO: 1668)

- J-H-1828-L6 GCAGGCCTTCTAGCAATTTACCCTT (SEQ ID NO: 1669)
- J-H-1828-U7 CGCTGACCGCCGCTGTCT (SEQ ID NO: 1670)
- J-H-1828-L7 CGCCGCAGCTGCACGTA (SEQ ID NO: 1671)
- J-H-1828-U8 CTCCTGGCCGCGTCTG (SEQ ID NO: 1672)
- 5 J-H-1828-L8 GGACCCCTCCGCTGACGA (SEQ ID NO: 1673)
- J-H-1828-L9 GCGCCGCAGCTGCACGTA (SEQ ID NO: 1674)
- J-H-1828-U10 GCCTGGGCGCCTTCTACG (SEQ ID NO: 1675)
- J-H-1828-L10 AGGTGCACGTGCGCCTC (SEQ ID NO: 1676)
- J-H-1828-U11 CCCCCTGCTGCGCCAAG (SEQ ID NO: 1677)
- 10 J-H-1828-L11 GCGTGGCCCGGAGCGTTT (SEQ ID NO: 1678)
- J-H-1828-U12 GGTCACGGCTGCCACGAACAT (SEQ ID NO: 1679)
- J-H-1828-L12 GCACGCGGAATTGGGATAAGG (SEQ ID NO: 1680)
- J-H-1828-L13 CTCTGCTGGGTGCCGGCTAAA (SEQ ID NO: 1681)
- 15 KIAA1828 cDNA sequence (SEQ ID NO: 2)
- AGCCCCGCAATCTGTTGATAACTCGGTCCCAGCTCGGCCGCTGCCCTCGCGAAT
 GGAGAGCGGGTCCCCGGCGGGGGGAGCGCAGCGCTGTGTCTCCGGGAGCGCG
 GCCCGGCCGCCCCGGCAGCCGCTTCGGCCACAGCAGATGGGAGCAGCTCCCGG
 ACTGCGCCCCGCCCCGCGCGGTCAACCCTGAGGCCAGGGGCCCCGGGAGCGCGAC
 20 CTCCTGGCCGCGCTGTGGGACTTTGACCTTCCAGAGGCCATGGAGGCTGGCGGG
 GAGCAGGGCGCCACCTGATCGCCTCCCCCTGGACGCCTCCTCCAGCGGCGTCA
 CGTTCCGCAACTTTGCAGCGCTCATGATCTGAAGACAGTGTCTCCTGCC
 CGCTACCCAGGGGAGTTCTTGCACCCCGTGGTGTACGCGTGACGGCCGTCATG
 CTGCTCTGCCTCCTGGCCTCCTTCGTACCTACATCGTGACCAAGAGCGCCATCC
 25 GCATCAGCCGCAAGGGCCGGCACACGCTCCTGAATTTCTGCTTCCACGCGGCC
 TGACCTTCACTGTGTTGCGCCGGCGGCATCAATCGCACCAAGTACCCATCCTGT
 GCCAGGCGGTGGGCATCGTGCTGCACTATTCTACACTGTCCACCATGCTGTGGA
 TAGGAGTGACCGCCAGGAACATCTACAAGCAGGTGACCAAGAAGGCCCTCTG
 TGCCTGGACACAGACCAGCCACCGTACCCAGGCAGCCCCTGCTCAGGTTTTAC
 30 CTCGTCAGCGGAGGGGTCCCCTTTATCATCTGTGGGGTCACGGCTGCCACGAAC
 ATCAGGAATTACGGGACAGAGGACGAGGACACGGCGTACTGCTGGATGGCCTG
 GGAGCCCAGCCTGGGCGCCTTCTACGGCCCAGCCGCCATCATACCCTGGTCAC
 CTGTGTGTACTTCTGGGCACCTACGTGCAGCTGCGGCGCCACCCAGGGCGCAG
 GTACGAGCTGCGCACACAGCCCGAGGAGCAGCGGCGGCTGGCGACACCCGAGG
 35 GCGGCCGTGGGATCCGGCCAGGCACCCACCCGCACACGATGCCCCGGCGCC
 TCCGTGCTGCAGAACGAGCACTCATTCAGGCACAGCTGCGCGCCGCCGCTTC
 ACGCTGTTCTGTTCACGGCCACGTGGGCCTTCGGGGCGCTGGCGGTGTCACAG

- GGCCACTTCCTGGACATGGTCTTCAGCTGCCTGTACGGCGCCTTCTGCGTGACC
 CTGGGACTCTTCGTGCTCATCCACCACTGCGCCAAGCGTGAGGACGTGTGGCAG
 TGCTGGTGGGCATGCTGCCCCCCCCGCAAGGACGCCCACCCCGCACTTGACGCC
 AACGGGGCCGCGCTGGGCGCGCCGCTGCCTGCACTCGCCGGGACTGGGCCA
 5 GCCACGGGGCTTCGCGCACCCACCGGGCCCCCTGCAAGATGACCAACCTGCAGG
 CCGCGCAGGGCCACGCCAGTTGCCTGTACCGGCCACCCCGTGCTGCGCCAAGA
 TGA CTGCGAGCCACTGACGGCGGACGAGGCGCACGTGCACCTGCAGGAGGAG
 GGCGCCTTCGGGCACGACCCCCACCTGCACGGGTGCCTTCAGGGCAGAACTAA
 GCCGCCCTACTTTAGCCGGCACCCAGCAGAGGAGCCCGAGTACGCCTACCACAT
 10 CCCATCCAGCCTGGATGGCAGCCCCCGCAGCTCGCGCACAGACAGCCCCCCCCA
 GCTCTCTGGATGGCCCCGGCGGGGACACACACGCTGGCCTGCTGCACCCAGGGC
 GACCCCTTCCCCATGGTCACCCAGCCCGAGGGCAGTGATGGGAGCCCTGCCCTC
 TACAGCTGCCCCACGCAGCCGGGACGGGAGGACGCGCTCGGGCCCCGGCCACTT
 GGAGATGCTGCGGAGGACACAGTCCCTGCCCTTTGGTGGCCCCAGCCAGAACG
 15 GGCTGCCCAAGGGTAAATTGCTAGAAAGGCCTGCCGTTTGGCACCCAGGGACC
 GGCAACATCCGAACGGGACCCTGGAAAAACGAACTACTGTG[TA]GATGGGGGGC
 AGAGGACACGGTGTTCTGAGGAGCTTCAGAGCAGAGTGGGGGGGCCATCTG
 CCACATGAGGTCACTGGGGGTACCGAAGTGACCCCGCCTTTC
- 20 KIAA1828 polypeptide sequence (SEQ ID NO: 1)
 MDLKTVLSLPRYPGEFLHPVVYACTAVMLLCLLASFVTVYVHQS AIRISRKGRHTLL
 NFCFHAALTFTVFAGGINRTKYPILCQAVGIVLHYSTLSTMLWIGVTARNIYKQVTK
 KAPLCLDTDQPPYPRQPLRFYLVSGGVFHCVTAA TNIRNYGTEDEDTAYCWM
 AWEPSLGAFYGPAAIITLVTCVYFLGTYVQLRRHPGRRYELRTQPEEQRRLATPEG
 25 GRGIRPGTPPAHDAPGASVLQNEHSFQAQLRAAAFTLFLTATWAFGALAVSQGHF
 LDMVFSCLYGAFCVTLGLFVLIHHC AKREDVWQCWWACCPPRKDAHPALDANGA
 ALGRAACLHSPGLGQPRGFAHPPGPCKMTNLQAAQGHASCLSPATPCCA KMHCEP
 LTAD EAHVHLQEEGAFGHDPHLHGCLQGR TKPPYFSRHPAEEPEYAYHIPSSLDGSP
 RSSRTD SPSSLDGPAGHTLACCTQGD PPFMTQPEGSDGSPALYSCPTQPGREAA
 30 LGPGHLEMLRRTQSLPFGGPSQNGLPKGKLLLEGLPFGTDGTGNIRTGPWKNETTV

Human HGPCR19

- Full length cDNA was isolated from human Whole brain by a combination of 5' and
 3' Rapid Amplification of cDNA Ends (RACE) and internal RT-PCR experiments as
 35 described above. RACE pituitary was prepared using the Invitrogen GeneRacer Kit (Cat #
 L1500-01).

The following RACE primers were used:

- 5' RACE (Invitrogen) CGACTGGAGCACGAGGACACTGA (SEQ ID NO: 1545)
 40 3' RACE (Invitrogen): GCTGTCAACGATACGCTACGTAACG (SEQ ID NO:
 1546)

5' nested RACE primer: GGACACTGACATGGACTGAAGGAGTA (SEQ ID NO: 1547)

3' nested RACE primer: CGCTACGTAACGGCATGACAGTG (SEQ ID NO: 1548)

5 The following cDNA primers were used:

- Hpg27-01up ATGACGCCCCAACAGCACTGGC (SEQ ID NO: 1582)
 Hpg27-01dn TGGCGGGCGCTGCTCATAG; (SEQ ID NO: 1583) used in 5' RACE
 Hpg27-01bn GGATGGCTGAGCTGGACGGAT (SEQ ID NO: 1584)
 Hpg27-02up TTACTGGTCCTGCCTCCTCGTCTAC (SEQ ID NO: 1585)
 10 Hpg27-02dn CAGTCAGTGCGGGGTCAAACA (SEQ ID NO: 1586)
 Hpg27-03up AGGCTATCTTCCCAGCCCCCTACCT; (SEQ ID NO: 1587) used in 3' RACE
 Hpg27-03dn CTTGCCTGCCTGGAGTCGGAC (SEQ ID NO: 1588)
 Hpg27-04up CTCCTCTCAGTCCTGGCCTATG (SEQ ID NO: 1589)
 15 Hpg27-04dn ACTTCCCAGAGACAGAGTCTGTGTG (SEQ ID NO: 1590)
 Hpg27-05up TGCTACCACACAGGACATATGTGTT (SEQ ID NO: 1591)
 Hpg27-05dn GAGCCCATAGACTTCGAGGTACAG (SEQ ID NO: 1592)
 Hpg27-06up CCTCAACACAGCTGCCCAGAAAAGG (SEQ ID NO: 1593)
 Hpg27-06dn GCTAGGAGCAGGTTTCGCGGTGAT (SEQ ID NO: 1594)
 20 Hpg27-07up TCCTCTGGCCGTTTATGATTAT (SEQ ID NO: 1595)
 Hpg27-07dn TGGAAAGGAGGAAGAGATACTAGTTAA (SEQ ID NO: 1596)

HGPCR19 nucleotide sequence (SEQ ID NO: 1063)

- ATGTTTAATTGGCAATTAATTGAAAAATTCTGTGTATCAGCGAACATGATACAG
 25 CCCACAGCCTGCGGGTCTGCGCCCCTGGATTAACATGCTGCCCTGCCAGGAGGA
 CACGACCTGCAGCCCCATCCTAACTCTGGCCACCCATCCTGCAGGCATGCCGG
 CTGCCGCTCCAGGACTCCCCTGTCCCCAGGACCAAGATGACGCCAACAGCACT
 GCGGAGGTGCCAGCCCCATTCCCAAGGGGGCTTTGGGGCTCTCCCTGGCCCTG
 GCAAGCCTCATCATCACCGCGAACCTGCTCCTAGCCCTGGGCATCGCCTGGGAC
 30 CGCCGCCTGCGCAGCCCACCTGCTGGCTGCTTCTCCTGAGCCTACTGCTGGCTG
 GGCTGCTCACGGGTCTGGCATTGCCACATTGCCAGGGCTGTGGAACCAGAGTC
 GCCGGGGTTACTGGTCCTGCCTCCTCGTCTACTTGGCTCCCAACTTCTCCTTCT
 CTCCCTGCTTGCCAACCTCTTGCTGGTGCACGGGGAGCGCTACATGGCAGTCCT
 GAGGCCACTCCAGCCCCCTGGGAGCATTGGCTGGCCCTGCTCCTCACCTGGGC

TGGTCCCCTGCTCTTTGCCAGTCTGCCCCGCTCTGGGGTGGAACCACTGGACCCCT
 GGTGCCAACTGCAGCTCCCAGGCTATCTTCCCAGCCCCCTACCTGTACCTCGAA
 GTCTATGGGCTCCTGCTGCCCCGCGTGGGTGCTGCTGCCTTCTCTGTCCGCG
 TGCTGGCCACTGCCCACCGCCAGCTGCAGGACATCTGCCGGCTGGAGCGGGCA
 5 GTGTGCCGCGATGAGCCCTCCGCCCTGGCCCGGGCCCTTACCTGGAGGCAGGCA
 AGGGCACAGGCTGGAGCCATGCTGCTCTTCGGGCTGTGCTGGGGGGCCCTACGTG
 GCCACACTGCTCCTCTCAGTCTGGCCTATGAGCAGCGCCCGCCACTGGGGCCCT
 GGGACACTGTTGTCCCTCCTCTCCCTAGGAAGTGCCAGTGCAGCGGCAGTGGCC
 GTAGCCATGGGGCTGGGCGATCAGCGCTACACAGCCCCCTGGAGGGCAGCCGC
 10 CCAAAGGTGCCTGCAGGGGCTGTGGGGAAGAGCCTCCCGGGACAGTCCCGGCC
 CCAGCATTGCCTACCACCCAAGCAGCCAAAGCAGTGTGACCTGGACTTGAACCT
 AAAGGAAGGGCCTCTGCTGACTCCTACCAGAGCATCCGTCCAGCTCAGCCATCC
 AGCCTGTCTCTACCGGGCCCCACTTCTCTGGATCAGAGACCCTGCCTCTGTTTGA
 CCCCCTGACTGACTGAATAAAGCTCCTCTGGCCGTTTATGATTATCTCATTCCATA
 15 TCTCAGGGCGAGGCAGGAGGAAATGGCTCAACACACCAACAATAGAAAGAACC
 TACAGACATACGCGTGGATTAAGGCAGAGTCCGACTCCAGGCAGGCAAGAAGT
 GTCGTGCGCACAGACCACCCCTGGAGATGGGGAGCTGGCACATCTCAACATCC
 AGCCGATTCTGCGGGACAGCCTTGCCCTGACGGGGCCCTCGCTAGCTCCTCCTA
 GGGTCCAGCCATCACAAAATCCACACAGACTCTGTCTCTGGGAAGTATATTTTA
 20 TTTACATTTTTTAAAATCTTAACTAGTATCTCTTCTCCTTTCCA

HGPCR19 polypeptide sequence (SEQ ID NO: 586)

MTPNSTGEVPSPIPKGALGLSLALASLIITANLLLALGIAWDRRLRSPAGCFFLSLLL
 AGLLTGLALPTLPGLWNQSRRGYWSCLLVYLAPNFSFLSLLANLLL VHGERYMAV
 25 LRPLQPPGSIRLALLLTWAGPLL FASLPALGWNHWTPGANCSSQAIFPAPYLYLEVY
 GLLLPVAGAAFLSVRVLATAHRQLQDICRLERAVCRDEPSALARALTWRQARAQ
 AGAMLLFGLCWGPYVATLLSVLAYEQRPLPGTLLSLLSLGSASAAVPVAMG
 LGDQRYTAPWRAAAQRCLQGLWGRASRDSPGPSIAYHPSSQSSVDLDLN

30 Human PGR24

Full length cDNA was isolated from human Amygdala and Pituitary by a
 combination of 5' and 3' Rapid Amplification of cDNA Ends (RACE) and internal
 RT-PCR experiments as described above. RACE pituitary was prepared using the
 Invitrogen GeneRacer Kit (Cat # L1500-01).

35

The following RACE primers were used:

5' RACE (Invitrogen) CGACTGGAGCACGAGGACACTGA (SEQ ID NO: 1545)

3' RACE (Invitrogen): GCTGTCAACGATACGCTACGTAACG (SEQ ID NO:
 1546)

5' nested RACE primer: GGACACTGACATGGACTGAAGGAGTA (SEQ ID NO: 1547)

3' nested RACE primer: CGCTACGTAACGGCATGACAGTG (SEQ ID NO: 1548)

5 The following cDNA primers were used:

HHpg147-1up AGATCTTTCACATCAGTAGCCAGA (SEQ ID NO: 1697)

HHpg147-1dn GGAAGTGCATTGCGACTGT (SEQ ID NO: 1698)

HHpg147-2up CCAAGGAGAGGAGAGGCGCAGTT (SEQ ID NO: 1699)

HHpg147-2dn GAAAGCACAGACAGGCTCCACCAG; (SEQ ID NO: 1700) used in 5'

10 RACE

HHpg147-3up TACCTGGACTCCACCGCCTGC (SEQ ID NO: 1701)

HHpg147-3dn CAGGGTGACCGCCACGATG (SEQ ID NO: 1702)

HHpg147-4up CTCTGTCATTTGTGGGCTGTGGC (SEQ ID NO: 1703)

HHpg147-4dn GGTGTTGGCAGTCAGCACGAAGA (SEQ ID NO: 1704)

15 HHpg147-5up GCTGCTGTGGAGGAAGGTGGTAG; (SEQ ID NO: 1705) used in 3' RACE

HHpg147-5dn GGCCCTCAGGATCAAATACGCTA (SEQ ID NO: 1706)

HHpg147-6up CTCAATGTGCACACAAATGCCAT (SEQ ID NO: 1707)

HHpg147-6dn GGCCCTCAGGATCAAATACGCTA (SEQ ID NO: 1708)

20 HHpg147-7up AGAGGAGAGGCGCAGTTGCTTAAC (SEQ ID NO: 1709)

HHpg147-7dn CATATCTGGGTCCAGATCTGCTGCT (SEQ ID NO: 1710)

HHpg147-8up GCCTCCAGACCTTCCGTCAT (SEQ ID NO: 1711)

HHpg147-8dn GCATAAACCAGGAAGATGTACAGCC (SEQ ID NO: 1712)

HHpg147-9up GGCTGTCACAGTCGCAATGCAC (SEQ ID NO: 1713)

25 HHpg147-9dn GGCTGGCACGGGACTTAAAGGA (SEQ ID NO: 1714)

N147-01up GGGCTGTACATCTTCCTGGTTTAT (SEQ ID NO: 1715)

N147-01adn AGGGAGTTCTAGGGCCATAGGT (SEQ ID NO: 1716)

N147-01bdn CGGGACTTAAAGGAGAGGATATGG (SEQ ID NO: 1717)

N147-03up CAGGTCCCAGCCCCCATATCC (SEQ ID NO: 1718)

30 N147-03dn TCCCACAGTACCCACCCTGCC (SEQ ID NO: 1719)

N147-04up TGGCTCTCAGAGGTACTCGCAGCA (SEQ ID NO: 1720)
 N147-04dn AAAGCACTTCTCCCTCAGCGGGTT (SEQ ID NO: 1721)
 N147-05up GGGCATGGGTGAATGACTTCGAG (SEQ ID NO: 1722)
 N147-05dn TCCTCCCAAGGGGTACTGCCTGGT (SEQ ID NO: 1723)

5

PGR24A amygdala nucleotide sequence (SEQ ID NO: 80)

AAGGAGAGGAGAGGGCGCAGTTGCTTAACTGCTCCCCGGTGATGGCTGCTTAGCT
 TGTTCCCAAGTTTTTCCACCTTCCACACCATGCTGGAATGACAGCCTGCACTCTCC
 TCCCTCTGCCTCCCCTCTGCCCCCTTCACTGTGACGCATGGTGGGCAATCCCCTG
 10 GTCCCTAAATGCAGAGTCCTTGGCGTCCCTCCATCCTCCTGGTCTCTCTCCTTT
 CCCATCCACACTCACAACCTGCCCCATGCCCTCAATCCACGCTCATGCACCTGC
 CCTGTCTCTGTCTCCTGCCTCCAGACCTTCCGTCATAAGCTGGTGGAGCCTGTCT
 GTGCTTTCTGGAACCTACAGGGGTGCCTGGGCCACACAGGCTGCTCCGTGGCTG
 CCCTGTACCTGGACTCCACCGCCTGCTTCTGCAACCACAGCACCAGCTTTGCCA
 15 TCCTGCTGCAAATCTATGAAGTACAGAGAGGCCCTGAGGAGGAGTCGCTGCTG
 AGGACTCTGTCAATTTGTGGGCTGTGGCGTGTCTTCTGCGCCCTCACCACCACCT
 TCTTGCTCTTCCCTGGTGGCCGGGGTCCCCAAGTCAGAGCGAACCACAGTCCACA
 AGAACCTCACCTTCTCCCTGGCCTCTGCCGAGGGCTTCCCTCATGACCAGCGAGT
 GGGCCAAGGCCAATGAGGTGGCATGTGTGGCTGTCACAGTCGCAATGCACTTCC
 20 TCTTTCTGGTGGCATTCTCCTGGATGCTGGTGGAGGGGCTGCTGCTGTGGAGGA
 AGGTGGTAGCTGTGAGCATGCACCCGGGCCCAGGCATGCGGCTCTACCACGCC
 ACAGGCTGGGGCGTGCCTGTGGGCATCGTGGCGGTCAACCTGGCCATGCTCCCC
 CATGACTACGTGGCCCCCGGACATTGCTGGCTCAATGTGCACACAAATGCCATC
 TGGGCCTTCGTGGGGCCTGTGCTCTTCGTGCTGACTGCCAACACCTGCATCCTG
 25 GCGCGTGTGGTAATGATCACCGTGTCCAGTGCCCGCCGCGCTGCCCGCATGTTG
 AGCCACAGCCCTGCCTGCAGCAGCAGATCTGGACCCAGATATGGGGCACGGT
 GAAGCCCGTGTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
 CCTGGTGCACCTGAGCCCCGCCTGGGCCTACGCTGCCGTGGGCCTCAACTCCAT
 CCAGGGGCTGTACATCTTCCCTGGTTTATGCTGCCTGCAATGAGGAGGTGCGGAG
 30 CGCCCTGCAGAGGATGGCTGAGAAGAAGGTGGCCGAGGTGCTCAGGGCACTGG
 GGGTGTGGGTGGGGGCGGGAGGCCCCAGAGCCAGGTCCCAGCCCCCATATCC
 TCTCCTTTAAGTCCCGTGCCAGCCCTGCCAGCTGGGGGACCAGCCTGAGGCCCC
 CAGGCCCCCTGGGAGGCAGCCCGAGGGAGCCCCATAGCCTTGGCTCCACCCCGG
 AGACAC

35

PGR24A amygdala polypeptide sequence (SEQ ID NO: 79)

MTACTLLPLPPLCPFTCDAWWAIPWSLKRVLGVPPSSWSLSFPIHTHNCPMPLNPR
 SCTCPVSVSCLQTFRHKLVPEPVCAFWNRYGAWATTGCSVAALYLDSTACFCNHST
 SFAILLQIYEVQRGPEEESLLRSLFSVVGCVSFCALTTTFLFLVAGVPKSERTTVHK
 40 NLTFSLASAEGFLMTSEWAKANEVACVAVTVAMHFLFLVAFSWMLVEGLLLWRK
 VVAVSMHPGPGMRLYHATGWGVPVGIVAVTLAMLPHDYVAPGHCWLVNHTNAI
 WAFVGPVLFVLTANTCILARVVMITVSSARRRARMMLSPQPCLOQQIWTQIWATVKP

VLVLLPVLGLTWLAGILVHLSPAWAYAAVGLNSIQGLYIFLVYAAACNEEVRSALQR
MAEKKVAEVLRALGVWVGAGGPQSQVPAPISSPLSPVPALPAGGPA

PGR24P Pituitary nucleotide sequence (SEQ ID NO: 1552)

5
AAGGAGAGGAGAGGCGCAGTTGCTTAACTGCTCCCCGGTGATGGCTGCTTAGCT
TGTTCCCAGTTTTTCCACCTTCCACACCATGCTGGAATGACAGCCTGCACTCTCC
TCCCTCTGCCTCCCCTCTGCCCCTTACCTGTGACGCATGGTGGGCAATCCCCTG
GTCCCTAAAATGCAGAGTCCTTGGCGTCCCTCCATCCTCCTGGTCTCTCTCCTTT
10 CCCATCCACACTCACAACCTGCCCCATGCCCCCTCAATCCACGCTCATGCACCTGC
CCTGTCTCTGTCTCCTGCCTCCAGACCTTCCGTCATAAGCTGGTGGAGCCTGTCT
GTGCTTTCTGGAACCTACAGGGGTGCCTGGGCCACCACAGGCTGCTCCGTGGCTG
CCCTGTACCTGGACTCCACCGCTGCTTCTGCAACCACAGCACCAGCTTTGCCA
TCCTGCTGCAAATCTATGAAGTACAGGCCTGGGTCTGCTGGCTGCCTGCTGCAC
15 TGTGGAGGCGAATGC₂GGCGTGGGGGGCCTTAGAGTCACCAGGGTCCCCAAGT
CAGAGCGAACCACAGTCCACAAGAACCTCACCTTCTCCCTGGCCTCTGCCGAGG
GCTTCTCATGACCAGCGAGTGGGCCAAGGCCAATGAGGTGGCATGTGTGGCT
GTCACAGTCGCAATGCACTTCTTCTGCTGGCATTCTCCTGGATGCTGGTGG
AGGGGCTGCTGCTGTGGAGGAAGGTGGTAGCTGTGAGCATGCACCCGGGCCCA
20 GGCATGCGGCTCTACCACGCCACAGGCTGGGGCGTGCCTGTGGGCATCGTGGC
GGTCACCCTGGCCATGCTCCCCCATGACTACGTGGCCCCCGGACATTGCTGGCT
CAATGTGCACACAAATGCCATCTGGGCCTTCGTGGGGCCTGTGCTCTTCGTGCT
GACTGCCAACACCTGCATCCTGGCCCCTGTGGTAATGATCACCGTGTCCAGTGC
CCGCCGCCGTGCCCGCATGTTGAGCCACAGCCCTGCCTGCAGCAGCAGATCTG
25 GACCCAGATATGGGCCACGGTGAAGCCCGTGTGGTCTGCTGCCCGTCTTAGG
CCTGACCTGGCTGGCAGGCATCCTGGTGCACCTGAGCCCCGCCTGGGCCTACGC
TGCCGTGGGCCTCAACTCCATCCAGGGGCTGTACATCTTCTGGTTTATGCTGCC
TGCAATGAGGAGGTGCGGAGCGCCCTGCAGAGGATGGCTGAGAAGAAGGTGGC
CGAGGTGCTCAGGGCACTGGGGGTGTGGGTGGGGGCGGGAGGCCCCCAAGAGCC
30 AGGTCCCAGCCCCCATATCCTCTCCTTTAAGTCCCGTGCCAGCCCTGCCAGCTG
GGGGACCAGCCTGAGGCCCCCAAGGCCCTGGGAGGCAGCCGAGGGAGCCCCA
TAGCCTTGGCTCCACCCCGGAGACAC

PGR24P Pituitary polypeptide sequence(SEQ ID NO: 1551)

35 MTACTLLPLPLCPFTCDAWWAIPWSLKCRVLGVPPSSWSLSFPIHTHNCPMPLNPR
SCTCPVSVSCLQTFRHLKLEPVCAFVWNYRGAWATTGCSVAALYLDSTACFCNHST
SFAILLQIYEVQAWVLLAACCTVEANAGVGGRLRVTRVPKSERTTVHKNLTFSLASA
EGFLMTSEWAKANEVACVAVTVAMHFLFLVAFSWMLVEGLLLWRKVAVSMHP
GPGMRLYHATGWGVPGVIVAVTLAMLPHDYVAPGHCWLVNVTNAIWAFVGPVL
40 FVLTANTCILARVVMITVSSARRRRARMLSPQPCLQQIWTQIWATVKPVLVLLPVL
GLTWLAGILVHLSPAWAYAAVGLNSIQGLYIFLVYAAACNEEVRSALQRMAEKKVA
EVLRALGVWVGAGGPQSQVPAPISSPLSPVPALPAGGPA

Table 1. GPCRs

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| KIAA1828 | 1 | 2 | 3 | 4 |
| PGR10 | 5 | 6 | 7 | 8 |
| PGR11 | 9 | 10 | 11 | 12 |
| PGR12 | 13 | 14 | 15 | 16 |
| PGR13 | 17 | 18 | 19 | 20 |
| PGR14 | 21 | 22 | 23 | 24 |
| PGR15 | 25 | 26 | 27 | 28 |
| PGR17 | 29 | 30 | 31 | 32 |
| PGR2 | 33 | 34 | 35 | 36 |
| PGR20 | 37 | 38 | 39 | 40 |
| PGR22 | 41 | 42 | 43 | 44 |
| PGR25 | 45 | 46 | 47 | 48 |
| PGR26 | 49 | 50 | 51 | 52 |
| PGR3 | 53 | 54 | 55 | 56 |
| PGR5 | 57 | 58 | 59 | 60 |
| PGR1 | 61 | 62 | 63 | 836 |
| PGR16 | 64 | 65 | 66 | 837 |
| PGR18 | 67 | 68 | 69 | 838 |
| PGR19 | 70 | 71 | 72 | 839 |
| PGR21 | 73 | 74 | 75 | 840 |
| PGR23 | 76 | 77 | 78 | 841 |
| PGR24A | 79 | 80 | - | - |
| PGR24P | 1551 | 1552 | - | - |
| PGR27 | 81 | 82 | 83 | 842 |
| PGR28 | 84 | 85 | 86 | 843 |
| PGR4 | 87 | 88 | 89 | 844 |
| PGR6 | 90 | 91 | - | - |
| PGR7 | 92 | 93 | 94 | 845 |
| PGR9 | 95 | 96 | - | - |
| AGR9 | 97 | 846 | 98 | 99 |
| BAI1 | 100 | 847 | 101 | 102 |
| BAI2 | 103 | 848 | 104 | 105 |
| BAI3 | 106 | 849 | 107 | 108 |
| DJ287G14 | 109 | 850 | 110 | 111 |
| DRD1 | 112 | 851 | 113 | 114 |
| DRD5 | 115 | 852 | 116 | 117 |
| EBI2 | 118 | 853 | 119 | 120 |
| FLJ14454 | 121 | 854 | 122 | 123 |
| GHSR | 124 | 855 | 125 | 126 |
| GIPR | 127 | 856 | 128 | 129 |
| GLP2R | 130 | 857 | 131 | 132 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| GPR101 | 133 | 858 | 134 | 135 |
| GPR103 | 136 | 859 | 137 | 138 |
| GPR17 | 139 | 860 | 140 | 141 |
| GPR20 | 142 | 861 | 143 | 144 |
| GPR21 | 145 | 862 | 146 | 147 |
| GPR23 | 148 | 863 | 149 | 150 |
| GPR25 | 151 | 864 | 152 | 153 |
| GPR26 | 154 | 865 | 155 | 156 |
| GPR37L1 | 157 | 866 | 158 | 159 |
| GPR39 | 160 | 867 | 161 | 162 |
| GPR4 | 163 | 868 | 164 | 165 |
| GPR48 | 166 | 869 | 167 | 168 |
| GPR51 | 169 | 870 | 170 | 171 |
| GPR58 | 172 | 871 | 173 | 174 |
| GPR62 | 175 | 872 | 176 | 177 |
| GPR64 | 178 | 873 | 179 | 180 |
| GPR68 | 181 | 874 | 182 | 183 |
| GPR82 | 184 | 875 | 185 | 186 |
| GPR92 | 187 | 876 | 188 | 189 |
| GRM2 | 190 | 877 | 191 | 192 |
| GRM4 | 193 | 878 | 194 | 195 |
| GRM5 | 196 | 879 | 197 | 198 |
| GRM6 | 199 | 880 | 200 | 201 |
| GRM7 | 202 | 881 | 203 | 204 |
| HCRTR1 | 205 | 882 | 206 | 207 |
| HCRTR2 | 208 | 883 | 209 | 210 |
| KIAA0758 | 211 | 884 | 212 | 213 |
| LEC1 | 214 | 885 | 215 | 216 |
| LEC2 | 217 | 886 | 218 | 219 |
| LEC3 | 220 | 887 | 221 | 222 |
| LGR6 | 223 | 888 | 224 | 225 |
| LGR7 | 226 | 889 | 227 | 228 |
| MTNR1B | 229 | 890 | 230 | 231 |
| NPFF1R | 232 | 891 | 233 | 234 |
| RE2 | 237 | 892 | 238 | 239 |
| SCTR | 240 | 893 | 241 | 242 |
| SREB3 | 243 | 894 | 244 | 245 |
| TAR2 | - | - | 246 | 247 |
| TAR3 | 248 | 895 | 249 | 250 |
| TM7SF1L2 | 251 | 896 | 252 | 253 |
| ADCYAP1R1 | 254 | 897 | 255 | 1188 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| ADMR | 256 | 898 | 257 | 1189 |
| ADORA1 | 258 | 899 | 259 | 1190 |
| ADORA2A | 260 | 900 | 261 | 1191 |
| ADORA2B | 262 | 901 | 263 | 1192 |
| ADORA3 | 264 | 902 | 265 | 1193 |
| ADRA1A | 266 | 903 | 267 | 1194 |
| ADRA1B | 268 | 904 | 269 | 1195 |
| ADRA1D | 270 | 905 | 271 | 1196 |
| ADRA2A | 272 | 906 | 273 | 1197 |
| ADRA2B | 274 | 907 | 275 | 1198 |
| ADRA2C | 276 | 908 | 277 | 1199 |
| ADRB1 | 278 | 909 | 279 | 1200 |
| ADRB2 | 280 | 910 | 281 | 1201 |
| ADRB3 | 282 | 911 | 283 | 1202 |
| AGTR1 | 284 | 912 | 285 | 1203 |
| AGTR2 | 286 | 913 | 287 | 1204 |
| AGTRL1 | 288 | 914 | 289 | 1205 |
| AVPR1A | 290 | 915 | 291 | 1206 |
| AVPR1B | 292 | 916 | 293 | 1207 |
| AVPR2 | 294 | 917 | 295 | 1208 |
| BDKRB1 | 296 | 918 | 297 | 1209 |
| BDKRB2 | 298 | 919 | 299 | 1210 |
| BLR1 | 300 | 920 | 301 | 1211 |
| BRS3 | 302 | 921 | 303 | 1212 |
| C3AR1 | 304 | 922 | 305 | 1213 |
| C5R1 | 306 | 923 | 307 | 1214 |
| CALCR | 308 | 924 | 309 | 1215 |
| CALCRL | 310 | 925 | 311 | 1216 |
| CASR | 312 | 926 | 313 | 1217 |
| CCBP2 | 314 | 927 | 315 | 1218 |
| CCKAR | 316 | 928 | 317 | 1219 |
| CCKBR | 318 | 929 | 319 | 1220 |
| CCR1 | 320 | 930 | 321 | 1221 |
| CCR2 | 322 | 931 | 323 | 1222 |
| CCR3 | 324 | 932 | 325 | 1223 |
| CCR4 | 326 | 933 | 327 | 1224 |
| CCR5 | 328 | 934 | 329 | 1225 |
| CCR6 | 330 | 935 | 331 | 1226 |
| CCR7 | 332 | 936 | 333 | 1227 |
| CCR8 | 334 | 937 | 335 | 1228 |
| CCR9 | 336 | 938 | 337 | 1229 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| CCRL1 | 338 | 939 | 339 | 1230 |
| CCXCR1 | 340 | 940 | 341 | 1231 |
| CD97 | 342 | 941 | 343 | 1232 |
| CELSR1 | 344 | 942 | 345 | 1233 |
| CELSR2 | 346 | 943 | 347 | 1234 |
| CELSR3 | 348 | 944 | 349 | 1235 |
| CHRM1 | 350 | 945 | 351 | 1236 |
| CHRM2 | 352 | 946 | 353 | 1237 |
| CHRM3 | 354 | 947 | 355 | 1238 |
| CHRM4 | 356 | 948 | 357 | 1239 |
| CHRM5 | 358 | 949 | 359 | 1240 |
| CMKLR1 | 360 | 950 | 361 | 1241 |
| CNR1 | 362 | 951 | 363 | 1242 |
| CNR2 | 364 | 952 | 365 | 1243 |
| CRHR1 | 366 | 953 | 367 | 1244 |
| CRHR2 | 368 | 954 | 369 | 1245 |
| CX3CR1 | 370 | 955 | 371 | 1246 |
| CXCR4 | 372 | 956 | 373 | 1247 |
| CXCR6 | 374 | 957 | 375 | 1248 |
| CYSLT1 | 376 | 958 | 377 | 1249 |
| CYSLT2 | 378 | 959 | 379 | 1250 |
| DRD2 | 380 | 960 | 381 | 1251 |
| DRD3 | 382 | 961 | 383 | 1252 |
| DRD4 | 384 | 962 | 385 | 1253 |
| EDG1 | 386 | 963 | 387 | 1254 |
| EDG2 | 388 | 964 | 389 | 1255 |
| EDG3 | 390 | 965 | 391 | 1256 |
| EDG4 | 392 | 966 | 393 | 1257 |
| EDG5 | 394 | 967 | 395 | 1258 |
| EDG6 | 396 | 968 | 397 | 1259 |
| EDG7 | 398 | 969 | 399 | 1260 |
| EDG8 | 400 | 970 | 401 | 1261 |
| EDNRA | 402 | 971 | 403 | 1262 |
| EDNRB | 404 | 972 | 405 | 1263 |
| EMR1 | 406 | 973 | 407 | 1264 |
| ETL | 408 | 974 | 409 | 1265 |
| F2R | 410 | 975 | 411 | 1266 |
| F2RL1 | 412 | 976 | 413 | 1267 |
| F2RL2 | 414 | 977 | 415 | 1268 |
| F2RL3 | 416 | 978 | 417 | 1269 |
| FKSG79 | 418 | 979 | 419 | 1270 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| FPR1 | 420 | 980 | 421 | 1271 |
| FSHR | 422 | 981 | 423 | 1272 |
| FY | 424 | 982 | 425 | 1273 |
| FZD10 | 426 | 983 | 427 | 1274 |
| FZD2 | 428 | 984 | 429 | 1275 |
| FZD3 | 430 | 985 | 431 | 1276 |
| FZD4 | 432 | 986 | 433 | 1277 |
| FZD5 | 434 | 987 | 435 | 1278 |
| FZD6 | 436 | 988 | 437 | 1279 |
| FZD7 | 438 | 989 | 439 | 1280 |
| FZD8 | 440 | 990 | 441 | 1281 |
| FZD9 | 442 | 991 | 443 | 1282 |
| G2A | 444 | 992 | 445 | 1283 |
| GABBR1 | 446 | 993 | 447 | 1284 |
| GALR1 | 448 | 994 | 449 | 1285 |
| GALR2 | 450 | 995 | 451 | 1286 |
| GALR3 | 452 | 996 | 453 | 1287 |
| GCGR | 454 | 997 | 455 | 1288 |
| GHRHR | 456 | 998 | 457 | 1289 |
| GLP1R | 458 | 999 | 459 | 1290 |
| GNRHR | 460 | 1000 | 461 | 1291 |
| GPCR150 | 462 | 1001 | 463 | 1292 |
| GPR1 | 464 | 1002 | 465 | 1293 |
| GPR10 | 466 | 1003 | 467 | 1294 |
| GPR102 | 468 | 1004 | - | - |
| GPR105 | 470 | 1005 | 471 | 1296 |
| GPR12 | 472 | 1006 | 473 | 1297 |
| GPR14 | 474 | 1007 | 475 | 1298 |
| GPR15 | 476 | 1008 | 477 | 1299 |
| GPR18 | 478 | 1009 | 479 | 1300 |
| GPR19 | 480 | 1010 | 481 | 1301 |
| GPR2 | 482 | 1011 | 483 | 1302 |
| GPR22 | 484 | 1012 | 485 | 1303 |
| GPR24 | 486 | 1013 | 487 | 1304 |
| GPR27 | 488 | 1014 | 489 | 1305 |
| GPR3 | 490 | 1015 | 491 | 1306 |
| GPR30 | 492 | 1016 | 493 | 1307 |
| GPR34 | 494 | 1017 | 495 | 1308 |
| GPR35 | 496 | 1018 | 497 | 1309 |
| GPR37 | 498 | 1019 | 499 | 1310 |
| GPR40 | 500 | 1020 | 501 | 1311 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| GPR41 | 502 | 1021 | 503 | 1312 |
| GPR43 | 504 | 1022 | 505 | 1313 |
| GPR44 | 506 | 1023 | 507 | 1314 |
| GPR45 | 508 | 1024 | 509 | 1315 |
| GPR49 | 510 | 1025 | 511 | 1316 |
| GPR50 | 512 | 1026 | 513 | 1317 |
| GPR54 | 514 | 1027 | 515 | 1318 |
| GPR55 | 516 | 1028 | 517 | 1319 |
| GPR56 | 518 | 1029 | 519 | 1320 |
| GPR57 | 520 | 1030 | 521 | 1321 |
| GPR6 | 522 | 1031 | 523 | 1322 |
| GPR61 | 524 | 1032 | 525 | 1323 |
| GPR63 | 526 | 1033 | 527 | 1324 |
| GPR65 | 528 | 1034 | 529 | 1325 |
| GPR66 | 530 | 1035 | 531 | 1326 |
| GPR7 | 532 | 1036 | 533 | 1327 |
| GPR73 | 534 | 1037 | 535 | 1328 |
| GPR73L1 | 536 | 1038 | 537 | 1329 |
| GPR74 | 538 | 1039 | 539 | 1330 |
| GPR75 | 540 | 1040 | 541 | 1331 |
| GPR77 | 542 | 1041 | 543 | 1332 |
| GPR80 | 544 | 1042 | 545 | 1333 |
| GPR81 | 546 | 1043 | 547 | 1334 |
| GPR83 | 548 | 1044 | 549 | 1335 |
| GPR84 | 550 | 1045 | 551 | 1336 |
| GPR85 | 552 | 1046 | 553 | 1337 |
| GPR86 | 554 | 1047 | 555 | 1338 |
| GPR87 | 556 | 1048 | 557 | 1339 |
| GPR88 | 558 | 1049 | 559 | 1340 |
| GPR9 | 560 | 1050 | 561 | 1341 |
| GPR91 | 562 | 1051 | 563 | 1342 |
| GPRC5B | 564 | 1052 | 565 | 1343 |
| GPRC5C | 566 | 1053 | 567 | 1344 |
| GPRC5D | 568 | 1054 | 569 | 1345 |
| GPRC6A | 570 | 1055 | 571 | 1346 |
| GRCA | 572 | 1056 | 573 | 1347 |
| GRM1 | 574 | 1057 | 575 | 1348 |
| GRM3 | 576 | 1058 | 577 | 1349 |
| GRM8 | 578 | 1059 | 579 | 1350 |
| GRPR | 580 | 1060 | 581 | 1351 |
| H963 | 582 | 1061 | 583 | 1352 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| HGPCR11 | 584 | 1062 | 585 | 1353 |
| HGPCR19 | 586 | 1063 | 587 | 1354 |
| HGPCR2 | 588 | 1064 | 589 | 1355 |
| HM74 | 590 | 1065 | 591 | 1356 |
| HRH1 | 592 | 1066 | 593 | 1357 |
| HRH2 | 594 | 1067 | 595 | 1358 |
| HRH3 | 596 | 1068 | 597 | 1359 |
| HRH4 | 598 | 1069 | 599 | 1360 |
| HTR1A | 600 | 1070 | 601 | 1361 |
| HTR1B | 602 | 1071 | 603 | 1362 |
| HTR1D | 604 | 1072 | 605 | 1363 |
| HTR1F | 606 | 1073 | 607 | 1364 |
| HTR2A | 608 | 1074 | 609 | 1365 |
| HTR2B | 610 | 1075 | 611 | 1366 |
| HTR2C | 612 | 1076 | 613 | 1367 |
| HTR4 | 614 | 1077 | 615 | 1368 |
| HTR5A | 616 | 1078 | 617 | 1369 |
| HTR6 | 618 | 1079 | 619 | 1370 |
| HTR7 | 620 | 1080 | 621 | 1371 |
| HUMNPIIY20 | 622 | 1081 | 623 | 1372 |
| IL8RA | 624 | 1082 | 625 | 1373 |
| IL8RB | 626 | 1083 | 627 | 1374 |
| LGR8 | 628 | 1084 | 629 | 1375 |
| LHCGR | 630 | 1085 | 631 | 1376 |
| LTB4R | 632 | 1086 | 633 | 1377 |
| LTB4R2 | 634 | 1087 | 635 | 1378 |
| MAS1 | 636 | 1088 | 637 | 1379 |
| MC1R | 638 | 1089 | 639 | 1380 |
| MC2R | 640 | 1090 | 641 | 1381 |
| MC3R | 642 | 1091 | 643 | 1382 |
| MC4R | 644 | 1092 | 645 | 1383 |
| MC5R | 646 | 1093 | 647 | 1384 |
| MRGD | 648 | 1094 | 649 | 1385 |
| MRGE | 650 | 1095 | 651 | 1386 |
| MRGF | 652 | 1096 | 653 | 1387 |
| MTNR1A | 654 | 1097 | 655 | 1388 |
| N8 (MRGG) | 656 | 1098 | 657 | 1389 |
| NMBR | 658 | 1099 | 659 | 1390 |
| NMU2R | 660 | 1100 | 661 | 1391 |
| NPY1R | 662 | 1101 | 663 | 1392 |
| NPY2R | 664 | 1102 | 665 | 1393 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| NPY5R | 666 | 1103 | 667 | 1394 |
| NPY6R | 668 | 1104 | 669 | 1395 |
| NTSR1 | 670 | 1105 | 671 | 1396 |
| NTSR2 | 672 | 1106 | 673 | 1397 |
| OA1 | 674 | 1107 | 675 | 1398 |
| OPN1MW | 676 | 1108 | 677 | 1399 |
| OPN1SW | 678 | 1109 | 679 | 1400 |
| OPN3 | 680 | 1110 | 681 | 1401 |
| OPN4 | 682 | 1111 | 683 | 1402 |
| OPRD1 | 684 | 1112 | 685 | 1403 |
| OPRK1 | 686 | 1113 | 687 | 1404 |
| OPRL1 | 688 | 1114 | 689 | 1405 |
| OPRM1 | 690 | 1115 | 691 | 1406 |
| OXTR | 692 | 1116 | 693 | 1407 |
| P2RY1 | 694 | 1117 | 695 | 1408 |
| P2RY12 | 696 | 1118 | 697 | 1409 |
| P2RY2 | 698 | 1119 | 699 | 1410 |
| P2RY4 | 700 | 1120 | 701 | 1411 |
| P2RY6 | 702 | 1121 | 703 | 1412 |
| P2Y10 | 704 | 1122 | 705 | 1413 |
| P2Y5 | 706 | 1123 | 707 | 1414 |
| PGR8 | 708 | 1124 | 709 | 1415 |
| PNR | 710 | 1125 | 711 | 1416 |
| PPYR1 | 712 | 1126 | 713 | 1417 |
| PTAFR | 714 | 1127 | 715 | 1418 |
| PTGDR | 716 | 1128 | 717 | 1419 |
| PTGER1 | 718 | 1129 | 719 | 1420 |
| PTGER2 | 720 | 1130 | 721 | 1421 |
| PTGER3 | 722 | 1131 | 723 | 1422 |
| PTGER4 | 724 | 1132 | 725 | 1423 |
| PTGFR | 726 | 1133 | 727 | 1424 |
| PTGIR | 728 | 1134 | 729 | 1425 |
| PTHR1 | 730 | 1135 | 731 | 1426 |
| PTHR2 | 732 | 1136 | 733 | 1427 |
| RAI3 | 734 | 1137 | 735 | 1428 |
| RDC1 | 736 | 1138 | 737 | 1429 |
| RGR | 738 | 1139 | 739 | 1430 |
| RHO | 740 | 1140 | 741 | 1431 |
| RRH | 742 | 1141 | 743 | 1432 |
| SALPR | 744 | 1142 | 745 | 1433 |
| SMOH | 746 | 1143 | 747 | 1434 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| SSTR1 | 748 | 1144 | 749 | 1435 |
| SSTR2 | 750 | 1145 | 751 | 1436 |
| SSTR3 | 752 | 1146 | 753 | 1437 |
| SSTR4 | 754 | 1147 | 755 | 1438 |
| SSTR5 | 756 | 1148 | 757 | 1439 |
| TACR1 | 758 | 1149 | 759 | 1440 |
| TACR2 | 760 | 1150 | 761 | 1441 |
| TACR3 | 762 | 1151 | 763 | 1442 |
| TAR1 | 764 | 1152 | 765 | 1443 |
| TAR4 | 766 | 1153 | 767 | 1444 |
| TBXA2R | 768 | 1154 | 769 | 1445 |
| TEM5 | 770 | 1155 | 771 | 1446 |
| TM7SF1 | 772 | 1156 | 773 | 1447 |
| TM7SF1L1 | 774 | 1157 | 775 | 1448 |
| TM7SF3 | 776 | 1158 | 777 | 1449 |
| TPRA40 | 778 | 1159 | 779 | 1450 |
| TRHR | 780 | 1160 | 781 | 1451 |
| TSHR | 782 | 1161 | 783 | 1452 |
| VIPR1 | 784 | 1162 | 785 | 1453 |
| VIPR2 | 786 | 1163 | 787 | 1454 |
| VLGR1 | 788 | 1164 | 789 | 1455 |
| CCRL2 | 790 | 1165 | 1554 | 1553 |
| EMR2 | 791 | 1166 | - | - |
| EMR3 | 792 | 1167 | - | - |
| FPRL1 | 793 | 1168 | - | - |
| FPRL2 | 794 | 1169 | - | - |
| FZD1 | 795 | 1170 | 1545 | 1546 |
| GNRHR2 | 796 | 1171 | - | - |
| GPR31 | 797 | 1172 | 1547 | 1548 |
| GPR32 | 798 | 1173 | - | - |
| GPR38 | 799 | 1174 | - | - |
| GPR52 | 800 | 1175 | - | - |
| GPR78 | 801 | 1176 | - | - |
| GPR8 | 802 | 1177 | - | - |
| HTR1E | 803 | 1178 | - | - |
| MRG | 804 | 1179 | - | - |
| MRGX1 | 805 | 1180 | - | - |
| MRGX2 | 806 | 1181 | - | - |
| MRGX3 | 807 | 1182 | - | - |
| MRGX4 | 808 | 1183 | - | - |
| OPN1LW | 809 | 1184 | 1549 | 1550 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| P2RY11 | 810 | 1185 | - | - |
| SLT | 811 | 1186 | - | - |
| TG1019 | 812 | 1187 | - | - |
| CMKBR1L1 | - | - | 813 | 1456 |
| CMKBR1L2 | - | - | 814 | 1457 |
| FPR-RS1 | - | - | 815 | 1458 |
| FPR-RS2 | - | - | 816 | 1459 |
| FPR-RS3 | - | - | 817 | 1460 |
| FPR-RS4 | - | - | 818 | 1461 |
| GPR33 | - | - | 819 | 1462 |
| GPR90 | - | - | 820 | 1463 |
| HTR5B | - | - | 821 | 1464 |
| MrgA1 | - | - | 822 | 1465 |
| MrgA2 | - | - | 823 | 1466 |
| MrgA3 | - | - | 824 | 1467 |
| MrgA4 | - | - | 825 | 1468 |
| MrgA5 | - | - | 826 | 1469 |
| MrgA6 | - | - | 827 | 1470 |
| MrgA7 | - | - | 828 | 1471 |
| MrgA8 | - | - | 829 | 1472 |
| MrgB1 | - | - | 830 | 1473 |
| MrgB2 | - | - | 831 | 1474 |
| MrgB3 | - | - | 832 | 1475 |
| MrgB4 | - | - | 833 | 1476 |
| MrgB5 | - | - | 834 | 1477 |
| TRHR2 | - | - | 835 | 1478 |
| F2RL | 1479 | 1480 | - | - |
| TA10 | - | - | 1481 | 1482 |
| TA11 | - | - | 1483 | 1484 |
| TA12 | - | - | 1485 | 1486 |
| TA14 | - | - | 1487 | 1488 |
| TA15 | - | - | 1489 | 1490 |
| HM74A | 1555 | 1556 | - | - |
| PGR15L | - | - | 1491 | 1492 |
| TA7 | - | - | 1493 | 1494 |
| TA8 | - | - | 1495 | 1496 |
| P2Y3L | 1497 | 1498 | 1499 | 1500 |
| TCP10C | - | - | 1501 | 1502 |
| GPR103L | - | - | 1503 | 1504 |
| OR51E1 | 1505 | 1515 | 1525 | 1535 |
| OR4N4 | 1506 | 1516 | 1526 | 1536 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| OR51Q1 | 1507 | 1517 | 1527 | 1537 |
| OR51E2 | 1508 | 1518 | 1528 | 1538 |
| OR8B3 | 1509 | 1519 | 1529 | 1539 |
| OR7D2 | 1510 | 1520 | 1530 | 1540 |
| OR2A7 | 1511 | 1521 | 1531 | 1541 |
| OR7E102 | 1512 | 1522 | 1532 | 1542 |
| OR2A1 | 1513 | 1523 | 1533 | 1543 |
| OR2I2 | 1514 | 1524 | 1534 | 1544 |

Table 2. Novel GPCRs

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| KIAA1828 | 1 | 2 | 3 | 4 |
| PGR10 | 5 | 6 | 7 | 8 |
| PGR11 | 9 | 10 | 11 | 12 |
| PGR12 | 13 | 14 | 15 | 16 |
| PGR13 | 17 | 18 | 19 | 20 |
| PGR14 | 21 | 22 | 23 | 24 |
| PGR15 | 25 | 26 | 27 | 28 |
| PGR17 | 29 | 30 | 31 | 32 |
| PGR2 | 33 | 34 | 35 | 36 |
| PGR20 | 37 | 38 | 39 | 40 |
| PGR22 | 41 | 42 | 43 | 44 |
| PGR25 | 45 | 46 | 47 | 48 |
| PGR26 | 49 | 50 | 51 | 52 |
| PGR3 | 53 | 54 | 55 | 56 |
| PGR5 | 57 | 58 | 59 | 60 |
| PGR1 | 61 | 62 | 63 | 836 |
| PGR16 | 64 | 65 | 66 | 837 |
| PGR18 | 67 | 68 | 69 | 838 |
| PGR19 | 70 | 71 | 72 | 839 |
| PGR21 | 73 | 74 | 75 | 840 |
| PGR23 | 76 | 77 | 78 | 841 |
| PGR24A | 79 | 80 | - | - |
| PGR24P | 1551 | 1552 | - | - |
| PGR27 | 81 | 82 | 83 | 842 |
| PGR28 | 84 | 85 | 86 | 843 |
| PGR4 | 87 | 88 | 89 | 844 |
| PGR6 | 90 | 91 | - | - |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| PGR7 | 92 | 93 | 94 | 845 |
| PGR9 | 95 | 96 | - | - |
| AGR9 | 97 | 846 | 98 | 99 |
| BAI1 | 100 | 847 | 101 | 102 |
| BAI2 | 103 | 848 | 104 | 105 |
| BAI3 | 106 | 849 | 107 | 108 |
| DJ287G14 | 109 | 850 | 110 | 111 |
| DRD1 | 112 | 851 | 113 | 114 |
| DRD5 | 115 | 852 | 116 | 117 |
| EBI2 | 118 | 853 | 119 | 120 |
| FLJ14454 | 121 | 854 | 122 | 123 |
| GHSR | 124 | 855 | 125 | 126 |
| GIPR | 127 | 856 | 128 | 129 |
| GLP2R | 130 | 857 | 131 | 132 |
| GPR101 | 133 | 858 | 134 | 135 |
| GPR103 | 136 | 859 | 137 | 138 |
| GPR17 | 139 | 860 | 140 | 141 |
| GPR20 | 142 | 861 | 143 | 144 |
| GPR21 | 145 | 862 | 146 | 147 |
| GPR23 | 148 | 863 | 149 | 150 |
| GPR25 | 151 | 864 | 152 | 153 |
| GPR26 | 154 | 865 | 155 | 156 |
| GPR37L1 | 157 | 866 | 158 | 159 |
| GPR39 | 160 | 867 | 161 | 162 |
| GPR4 | 163 | 868 | 164 | 165 |
| GPR48 | 166 | 869 | 167 | 168 |
| GPR51 | 169 | 870 | 170 | 171 |
| GPR58 | 172 | 871 | 173 | 174 |
| GPR62 | 175 | 872 | 176 | 177 |
| GPR64 | 178 | 873 | 179 | 180 |
| GPR68 | 181 | 874 | 182 | 183 |
| GPR82 | 184 | 875 | 185 | 186 |
| GPR92 | 187 | 876 | 188 | 189 |
| GRM2 | 190 | 877 | 191 | 192 |
| GRM4 | 193 | 878 | 194 | 195 |
| GRM5 | 196 | 879 | 197 | 198 |
| GRM6 | 199 | 880 | 200 | 201 |
| GRM7 | 202 | 881 | 203 | 204 |
| HCRTR1 | 205 | 882 | 206 | 207 |
| HCRTR2 | 208 | 883 | 209 | 210 |
| KIAA0758 | 211 | 884 | 212 | 213 |

| Gene Name | Human Polypeptide SEQ ID NO: | Human Polynucleotide SEQ ID NO: | Mouse Polypeptide SEQ ID NO: | Mouse Polynucleotide SEQ ID NO: |
|-----------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| LEC1 | 214 | 885 | 215 | 216 |
| LEC2 | 217 | 886 | 218 | 219 |
| LEC3 | 220 | 887 | 221 | 222 |
| LGR6 | 223 | 888 | 224 | 225 |
| LGR7 | 226 | 889 | 227 | 228 |
| MTNR1B | 229 | 890 | 230 | 231 |
| NPFF1R | 232 | 891 | 233 | 234 |
| PGR15L | - | - | 1491 | 1492 |
| RE2 | 237 | 892 | 238 | 239 |
| SCTR | 240 | 893 | 241 | 242 |
| SREB3 | 243 | 894 | 244 | 245 |
| TAR2 | - | - | 246 | 247 |
| TAR3 | 248 | 895 | 249 | 250 |
| TM7SF1L2 | 251 | 896 | 252 | 253 |

Polypeptide Expression and Purification

Recombinant GPCR polypeptides may be produced using standard techniques

- 5 known in the art. Such recombinant GPCR polypeptides are, for example, useful in *in vitro* assays for identifying therapeutic compounds.

- Accordingly, the present invention relates to expression systems that include a polynucleotide of the present invention, host cells that are genetically engineered with such expression systems, and production of polypeptides of the invention by recombinant
- 10 techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

- For recombinant production, host cells can be genetically engineered to incorporate expression systems or portions thereof for any polynucleotide of the present invention. Polynucleotides may be introduced into host cells by methods described in standard
- 15 laboratory manuals. Preferred methods of introducing polynucleotides into host cells include, for instance, calcium phosphate transfection, DEAE-dextran mediated transfection, transfection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, ballistic introduction, infection or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts.

A great variety of expression systems can be used. These include, without limitation, chromosomal, episomal, and virus-derived systems such as vector derived bacterial plasmids, bacteriophage, transposons, yeast episomes, insertion elements, yeast
5 chromosomal elements, viruses (such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses, and retroviruses), and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements, such as cosmids and phagemids. Preferred expression vectors include, but are not limited to, pcDNA3 (Invitrogen) and pSVL (Pharmacia
10 Biotech). Other expression vectors include, but are not limited to, pSPORTTm vectors, pGEMTm vectors (Promega), pPROEXvectorsTm (LTI, Bethesda, MD), BluescriptTm vectors (Stratagene), pQETm vectors (Qiagen), pSE420Tm (Invitrogen), and pYES2Tm(Invitrogen). The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector that is able to maintain,
15 propagate, or express a polynucleotide to produce a polypeptide in a host may be used. The appropriate polynucleotide may be inserted into an expression system by any of a variety of well-known and routine techniques, including transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts. Expression systems of the invention include bacterial, yeast, fungal, plant,
20 insect, invertebrate, vertebrate, and mammalian cells systems.

If a eukaryotic expression vector is employed, then the appropriate host cell would be any eukaryotic cell capable of expressing the cloned sequence. Preferably, eukaryotic cells are cells of higher eukaryotes. Suitable eukaryotic cells include, but are not limited to, non-human mammalian tissue culture cells and human tissue culture cells. Preferred host
25 cells include, but are not limited to, insect cells, HeLa cells, Chinese hamster ovary cells (CHO cells), African green monkey kidney cells (COS cells), human 293 cells, murine embryonal stem (ES) cells and murine 3T3 fibroblasts. Propagation of such cells in cell culture has become a routine procedure (see, Tissue Culture, Academic Press, Kruse and Patterson, eds. (1973), which is incorporated herein by reference in its entirety). In
30 addition, a yeast host may be employed as a host cell. Preferred yeast cells include, but are

not limited to, the genera, *Saccharomyces*, *Pichia*, and *Kluveromyces*. Preferred yeast hosts are *S. cerevisiae* and *P. pastoris*. Preferred yeast vectors can contain an origin of replication sequence from a 2T yeast plasmid, an autonomously replication sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a selectable marker gene. Shuttle vectors for replication in both yeast and *E. coli* are also included herein.

Alternatively, insect cells may be used as host cells. In a preferred embodiment, the polypeptides of the invention are expressed using a baculovirus expression system (see, Luckow et al., *BioTechnology*, 1988, 6. and *Baculovirus Expression Vectors: A Laboratory Manual*, O'Rielly et al. (Eds.), W.H. Freeman and Company, New York, 1992, each of which is incorporated herein by reference in its entirety). In addition, the Bac-to-Bac™ complete baculovirus expression system (Invitrogen) can, for example, be used for production in insect cells.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase.

Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B. and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S- transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

If a polypeptide of the present invention is to be expressed for use in screening assays, it may be produced at the surface of the cell. In this event, the cells may be harvested

prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

Polypeptides of the present invention can be recovered and purified from
5 recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxyapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well-known techniques
10 for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during intracellular synthesis, isolation, and/or purification.

Recombinant GPCR polypeptides (or alternatively, GPCR polypeptides isolated from an organism) may be targeted to the cell membrane. Membrane bound GPCR can be prepared by expressing the GPCR in a suitable cell or cell line, e.g., *Pichia pastoris* cells,
15 oocytes, or COS cells. Membranes containing the recombinant polypeptide may then be isolated from other cellular components by standard methods known in the art.

Expression of GPR 85 or other GPCR listed in Table 1.

Recombinant expression of GPR85 or other GPCR encoding polynucleotide listed in
20 Table 1 is expressed in a suitable host cell using a suitable expression vector by standard genetic engineering techniques. For example, the GPR85 is subcloned into the commercial expression vector pcDNA3.1 (Invitrogen, San Diego, CA) and transfected into Chinese Hamster Ovary (CHO) cells using the transfection reagent FuGENE6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert. Other eukaryotic
25 cell lines, including human embryonic kidney (HEK293) and COS cells, are suitable as well. Cells stably expressing GPCR are selected by growth in the presence of 100 µg/ml zeocin (Stratagene, LaJolla, CA). Optionally, GPR85 may be purified from the cells using standard chromatographic techniques. To facilitate purification, antisera, is raised against one or more synthetic peptide sequences that correspond to portions of the GPR85 amino
30 acid sequence, and the antisera is used to affinity purify GPCR. GPR85 also may be

expressed in-frame with a tag sequence (e.g., polyhistidine, hemagglutinin, FLAG) to facilitate purification. Moreover, it will be appreciated that many of the uses for GPCR polypeptides, such as assays described below, do not require purification of GPCR from the host cell.

- 5 Expression of GPCR in 293 cells. For expression of GPCR polypeptides in mammalian cells HEK293 (transformed human, primary embryonic kidney cells), a plasmid bearing the relevant GPCR coding sequence is prepared (Table 1), using vector pcDNA3.1 (Invitrogen). The forward primer for amplification of this GPCR cDNA is determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce the HindIII
- 10 cloning site and nucleotides matching the GPCR sequence. The reverse primer is also determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce an XbaI restriction site for cloning and nucleotides corresponding to the reverse complement of the GPCR sequence. The PCR product is gel purified and cloned into the HindIII-XbaI sites of the vector.
- 15 The expression vector containing the GPCR gene is purified using Qiagen chromatography columns and transfected into 293 cells using DOTAPTM transfection media (Boehringer Mannheim, Indianapolis, IN). Transiently transfected cells are tested for expression after 24 hours of transfection, using western blots probed with anti-His and anti-GPCR peptide antibodies. Permanently transfected cells are selected with Zeocin and
- 20 propagated. Production of the recombinant protein is detected from both cells and media by western blots probed with anti-His, or anti-GPCR peptide antibodies.
- Expression of GPCR in COS cells. For expression of the GPCR in COS7 cells, a polynucleotide molecule having a sequence selected from the group consisting of polynucleotide sequences listed in Table 1, can be cloned into vector p3-CI. This vector is a
- 25 pUC1 8-derived plasmid that contains the HCMV (human cytomegalovirus) promoter-intron located upstream from the bGH (bovine growth hormone) polyadenylation sequence and a multiple cloning site. In addition, the plasmid contains the DHFR (dihydrofolate reductase) gene which provides selection in the presence of the drug methotrexane (MTX) for selection of stable transformants.

The forward primer is determined by routine procedures and preferably contains a 5' extension which introduces an XbaI restriction site for cloning, followed by nucleotides which correspond to a sequence selected from the group consisting of sequences listed in Table 1. The reverse primer is also determined by routine procedures and preferably contains 5' extension of nucleotides which introduces a restriction cloning site followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of sequences listed in Table 1. The PCR reaction is performed as described in the manufactures instructions. The PCR product is gel purified and ligated into the p3-C1 vector. This construct is transformed into E. coli cells for amplification and DNA purification. The expression vector containing the GPCR polynucleotide sequence is purified with Qiagen chromatography columns and transfected into COS 7 cells using Lipofectamine[™] reagent from BRL, following the manufacturer's protocols. Forty-eight and 72 hours after transfection, the media and the cells are tested for recombinant protein expression. GPCR expressed from a COS cell culture can be purified by concentrating the cell- growth media to about 10 mg of protein/ml, and purifying the protein by chromatography.

Expression of GPCR in Insect Cells. For expression of GPCR in a baculovirus system, a polynucleotide molecule having a sequence selected from the group consisting of sequences listed in Table 1, can be amplified by PCR. The forward primer is determined by routine procedures and preferably contains a 5' extension which adds the NdeI cloning site, followed by nucleotides which correspond to a sequence selected from the group consisting of sequences listed in Table 1. The reverse primer is also determined by routine procedures and preferably contains a 5' extension which introduces the KpnI cloning site, followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of sequences listed in Table 1.

The PCR product is gel purified, digested with NdeI and KpnI, and cloned into the corresponding sites of vector pACHTL-A (Pharmingen, San Diego, CA). The pACHTL-A expression vector contains the strong polyhedrin promoter of the Autographa californica nuclear polyhedrosis virus (AcMNPV), and a 6xHis tag upstream from the multiple cloning site. A protein kinase site for phosphorylation and a thrombin site for excision of the

- recombinant protein precede the multiple cloning site is also present. Of course, many other baculovirus vectors could be used in place of pAcHTL-A, such as pAc373, pVL941 and pAcIML. Other suitable vectors for the expression of GPCR polypeptides can be used, provided that the vector construct includes appropriately located signals for transcription, translation, and trafficking, such as an in-frame AUG and a signal peptide, as required. Such vectors are described in Luckow et al., Virology 170:31-39, among others. The virus is grown and isolated using standard baculovirus expression methods, such as those described in Summers et al. (A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agricultural Experimental Station Bulletin No. 1555 (1987)).
- 5 In a preferred embodiment, pAcHLT-A containing a GPCR gene is introduced into baculovirus using the "BaculoGold™" transfection kit (Pharmingen, San Diego, CA) using methods established by the manufacturer. Individual virus isolates are analyzed for protein production by radiolabeling infected cells with 35S-methionine at 24 hours post infection. Infected cells are harvested at 48 hours post infection, and the labeled proteins are
- 10 visualized by SDS-PAGE. Viruses exhibiting high expression levels can be isolated and used for scaled up expression.

- For expression of a GPCR polypeptide in a Sf9 cells, a polynucleotide molecule having a sequence selected from the group consisting of sequences listed in Table 1, can be amplified by PCR using the primers and methods described above for baculovirus expression. The GPCR cDNA is, cloned into vector pAcHLT-A (Pharmingen) for expression in Sf9 insect cells. The insert is cloned into the NdeI and KpnI sites, after elimination of an internal NdeI site (using the same primers described above for expression in baculovirus). DNA is purified with Qiagen chromatography columns and expressed in Sf9 cells. Preliminary Western blot experiments from non-purified plaques are tested for the
- 20 presence of the recombinant protein of the expected size which reacted with the GPCR-specific antibody.

GPCR Expression Profiles: Related Diseases and Disorders

- Expression profiles for GPCRs of the present invention were determined with human and mice tissues using RT-PCR and tissue *in situ* hybridization methods. Our
- 30

findings are summarized below.

Methods

RT-PCR

5 *Tissue harvesting:* 8-10 week old male or female 129S1/SvIMJ mice (Jackson Laboratory) were used for tissue harvesting. Peripheral tissues were dissected fresh and stored in RNAlater at 4°C (Ambion). Some tissues were also purchased from PelFreez and kept frozen at -80°C until RNA extraction. Brains were removed and stored overnight at 4°C in RNAlater, then microdissected under a Leica MZ6 dissecting microscope into nine
10 regions, using landmarks from a mouse atlas.

RNA preparation: RNA was extracted using the Totally RNA kit (Ambion) including LiCl precipitation and DNase (Epicenter) treatment. To test for genomic DNA contamination, intron/exon spanning PCR primers for several genes (ApoAI, Nurr1, Actin, G3PDH and Blue opsin) were used in RT-PCRs, performed in the presence or absence of
15 RT, with 200ng of input cDNA.

RT reactions: 5µg of each RNA sample was reverse transcribed with random primers (Roche) in a 40µl reaction with 40U MMLV-RT (Roche) and 20U RNase inhibitor (Roche). cDNAs were treated with RNase H (Epicenter) and RNase A (Ambion) and normalized with 18S RNA primer sets (Ambion).

20 *PCRs:* Gene amplification was carried out in 25µl reactions with 2ng, 20ng or 200ng of input cDNA, in the presence of 1.25 U of AmpliTaq Gold Polymerase (Applied Biosystems) and 0.25µM of each primer. Cycling conditions were: 94°C for 5 minutes, followed by 37 or 40 cycles of 94°C / 0.5 minute - 65°C / 0.5 minute - 72°C / 1 minute. Subsequently to the final cycle, reactions were extended for 7 minutes at 72°C. All PCR
25 products were analyzed on a 2% agarose gel containing ethidium bromide and visualized on an Alpha Imager. Scanning was performed on an Alpha Imager by the Alpha Ease Program (Alpha Innotech).

Primers: Primers were designed using the Oligo 6.0 program (Mol. Bio. Insights). Their specificity was evaluated by BLAST searches of the human and mouse genomes and
30 confirmed by sequencing the bands obtained from RT-PCR.

In Situ Hybridization

Tissue dissection and sectioning: 8-10 week old male 129S1/SvIMJ mice (Jackson Laboratory) were sacrificed and their brains were dissected, snap frozen on dry ice, and
5 stored at -70°C . Brains were sectioned at 10-14 μm onto microscope slides. Sections were collected in series so that each gene was sampled at 100 μm intervals through the hypothalamus and amygdala, and at 500 μm intervals through the remainder of the brain.

Riboprobe preparation: T3 (sense) and T7 (antisense) promoters were attached to either side of the gene of interest and amplified by PCR, using primers with the
10 corresponding gene and promoter sequences. Transcription reactions were performed using Ambion Maxiscript kits. PCR generated templates (500ng) were added to 100 μCi of dried down ^{33}P -UTP (Perkin Elmer) in 10 μl reactions.

Hybridization: Prehybridization and hybridization reactions were performed as previously described, with modifications. Briefly, ^{33}P labeled riboprobes ($\sim 5 \times 10^6$ cpm/slide)
15 were applied to slides overnight at 55°C . Slides were then digested with RNase and rinsed in SSC, with a final rinse in 0.1X SSC at 70°C for 30min. Slides were subsequently dipped in NTB-2 emulsion, and developed after 3 weeks.

Analysis: Specific mRNA distributions were determined by examination of two complete brains for each gene, with light and darkfield microscopy. An additional brain
20 was examined for sense labeling, to assess sites of non-specific signal. Specific signal was scored as clusters of silver grains over discrete cells or brain regions, without corresponding signal in sense slides. Sections were counterstained with cresyl violet for contrast and regional identification. Images were captured with a Photometric CoolSnap camera and Universal Imaging MetaMorph software (both Meridian Instruments).

25

Expression Profile Results

We have determined the expression pattern for GPCRs, providing functional information for these receptors (Table 1). In addition, we have identified several new

GPCRs (Table 2). The GPCR polypeptides and polynucleotides may be relevant for the treatment or diagnosis of various disease or disorders, particularly behavioral disorders. In addition to the wild-type GPCR polypeptide, polymorphic, splice variant, mutagenized, and recombinant forms of a GPCR polypeptide may also be targets for treatment or diagnosis of diseases and disorders or for assaying for therapeutic compounds.

Nervous system tissues

Hypothalamus. GPCRs expressed in the hypothalamus are listed in Table 3. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the hypothalamus. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease involving the hypothalamus, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 3. GPCRs Expressed in the Hypothalamus

| | | | | | |
|-----------|----------|---------|---------|--------|--------|
| ADCYAP1R1 | CMKBR1L2 | GIPR | GPR73L1 | LEC1 | PGR17 |
| ADMR | CMKLR1 | GLP1R | GPR74 | LEC2 | PGR18 |
| ADORA1 | CNR1 | GLP2R | GPR75 | LEC3 | PGR20 |
| ADORA2A | CNR2 | GNRHR | GPR77 | LGR6 | PGR21 |
| ADORA2B | CRHR1 | GPCR150 | GPR80 | LGR7 | PGR22 |
| ADORA3 | CRHR2 | GPR1 | GPR81 | LGR8 | PGR23 |
| ADRA1A | CX3CR1 | GPR10 | GPR82 | LHCGR | PGR25 |
| ADRA1D | CXCR4 | GPR101 | GPR83 | LTB4R | PGR26 |
| ADRA2A | CXCR6 | GPR103 | GPR84 | LTB4R2 | PGR27 |
| ADRA2B | CYSLT1 | GPR105 | GPR85 | MAS1 | PGR28 |
| ADRA2C | DJ287G14 | GPR12 | GPR86 | MC2R | PGR3 |
| ADRB1 | DRD1 | GPR14 | GPR87 | MC3R | PGR4 |
| ADRB2 | DRD2 | GPR15 | GPR88 | MC4R | PGR5 |
| AGR9 | DRD3 | GPR17 | GPR90 | MC5R | PGR7 |
| AGTR1 | DRD4 | GPR18 | GPR92 | MRG | PGR8 |
| AGTR2 | DRD5 | GPR19 | GPRC5B | MRGE | PTAFR |
| AGTRL1 | EBI2 | GPR2 | GPRC5C | MRGF | PTGDR |
| AVPR1A | EDG1 | GPR20 | GPRC5D | MTNR1A | PTGER1 |
| AVPR2 | EDG2 | GPR21 | GRCA | NMBR | PTGER2 |
| BAI1 | EDG3 | GPR22 | GRM1 | NMU2R | PTGER3 |

| | | | | | |
|--------|---------|---------|-----------|--------|----------|
| BAI2 | EDG4 | GPR23 | GRM2 | NPFF1R | PTGER4 |
| BAI3 | EDG5 | GPR24 | GRM3 | NPY1R | PTGFR |
| BDKRB1 | EDG7 | GPR26 | GRM4 | NPY2R | PTHR1 |
| BDKRB2 | EDG8 | GPR27 | GRM5 | NPY5R | PTHR2 |
| BLR1 | EDNRA | GPR30 | GRM7 | NPY6R | RAI3 |
| BRS3 | EDNRB | GPR31 | GRM8 | NTSR1 | RDC1 |
| C3AR1 | EMR1 | GPR34 | GRPR | NTSR2 | RE2 |
| C5R1 | ETL | GPR35 | H963 | OA1 | RHO |
| CALCR | F2R | GPR37 | HCRT1 | OPN1MW | RRH |
| CALCRL | F2RL1 | GPR37L1 | HCRT2 | OPN1SW | SALPR |
| CASR | F2RL2 | GPR4 | HGPCR11 | OPN3 | SCTR |
| CCBP2 | F2RL3 | GPR43 | HGPCR2 | OPRD1 | SMOH |
| CCKAR | FKSG79 | GPR44 | HM74 | OPRK1 | SREB3 |
| CCKBR | FPR1 | GPR45 | HRH1 | OPRL1 | SSTR1 |
| CCR1 | FPR-RS2 | GPR48 | HRH2 | OPRM1 | SSTR2 |
| CCR2 | FY | GPR49 | HRH3 | OXTR | SSTR3 |
| CCR4 | FZD1 | GPR50 | HTR1A | P2RY1 | SSTR4 |
| CCR5 | FZD10 | GPR51 | HTR1B | P2RY12 | SSTR5 |
| CCR6 | FZD2 | GPR54 | HTR1D | P2RY2 | TACR1 |
| CCR8 | FZD3 | GPR55 | HTR1F | P2RY4 | TACR3 |
| CCR9 | FZD4 | GPR56 | HTR2A | P2RY6 | TBXA2R |
| CCRL1 | FZD5 | GPR6 | HTR2B | P2Y10 | TEM5 |
| CD97 | FZD6 | GPR61 | HTR2C | P2Y5 | TM7SF1 |
| CELSR1 | FZD7 | GPR62 | HTR4 | PGR1 | TM7SF1L1 |
| CELSR2 | FZD8 | GPR63 | HTR5A | PGR10 | TM7SF1L2 |
| CELSR3 | G2A | GPR64 | HTR6 | PGR11 | TM7SF3 |
| CHRM1 | GABBR1 | GPR65 | HTR7 | PGR12 | TPRA40 |
| CHRM2 | GALR1 | GPR66 | HUMNP1Y20 | PGR13 | TRHR |
| CHRM3 | GALR2 | GPR68 | IL8RA | PGR14 | TRHR2 |
| CHRM4 | GALR3 | GPR7 | KIAA0758 | PGR15 | VIPR2 |
| CHRM5 | GHSR | GPR73 | KIAA1828 | PGR16 | VLGR1 |

Amygdala. GPCRs expressed in the amygdala are listed in Table 4. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the amygdala. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of disease, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 4. GPCRs Expressed in the Amygdala

| | | | | | |
|-----------|----------|---------|-----------|--------|----------|
| ADCYAP1R1 | CNR1 | GPR10 | GPR81 | LEC1 | PGR20 |
| ADMR | CRHR1 | GPR101 | GPR82 | LEC2 | PGR21 |
| ADORA1 | CRHR2 | GPR103 | GPR83 | LEC3 | PGR22 |
| ADORA2A | CX3CR1 | GPR105 | GPR84 | LGR7 | PGR25 |
| ADORA2B | CXCR6 | GPR12 | GPR85 | LHCGR | PGR28 |
| ADORA3 | DJ287G14 | GPR14 | GPR86 | LTB4R | PGR3 |
| ADRA1A | DRD1 | GPR15 | GPR87 | MAS1 | PGR7 |
| ADRA1D | DRD2 | GPR17 | GPR88 | MC2R | PTAFR |
| ADRA2A | DRD5 | GPR19 | GPR9 | MC3R | PTGDR |
| ADRA2C | EBI2 | GPR2 | GPR92 | MC4R | PTGER1 |
| ADRB1 | EDG1 | GPR21 | GPRC5B | MC5R | PTGER2 |
| ADRB2 | EDG2 | GPR22 | GPRC5C | MRG | PTGER3 |
| AGR9 | EDG4 | GPR23 | GRCA | MRGE | PTGER4 |
| AGTR1 | EDG5 | GPR24 | GRM1 | MRGF | PTHR1 |
| AGTR2 | EDG7 | GPR26 | GRM2 | NMBR | PTHR2 |
| AGTRL1 | EDG8 | GPR27 | GRM3 | NMU2R | RAI3 |
| BAI1 | EDNRA | GPR3 | GRM4 | NPFF1R | RDC1 |
| BAI2 | EDNRB | GPR30 | GRM5 | NPY2R | RE2 |
| BAI3 | EMR1 | GPR34 | GRM7 | NPY5R | SALPR |
| BRS3 | ETL | GPR37 | GRM8 | NTSR1 | SCTR |
| C5R1 | F2R | GPR37L1 | GRPR | NTSR2 | SMOH |
| CALCRL | F2RL2 | GPR4 | H963 | OPN1MW | SREB3 |
| CASR | FPR1 | GPR45 | HCRT1 | OPN3 | SSTR1 |
| CCBP2 | FPR-RS2 | GPR48 | HCRT2 | OPRD1 | SSTR2 |
| CCKBR | FY | GPR50 | HRH1 | OPRK1 | SSTR3 |
| CCR5 | FZD1 | GPR51 | HRH2 | OPRL1 | SSTR4 |
| CCR6 | FZD10 | GPR54 | HRH3 | OPRM1 | SSTR5 |
| CCR9 | FZD2 | GPR55 | HTR1A | OXTR | TACR1 |
| CCRL1 | FZD3 | GPR56 | HTR1B | P2RY1 | TACR2 |
| CD97 | FZD4 | GPR6 | HTR1D | P2RY12 | TACR3 |
| CELSR1 | FZD5 | GPR61 | HTR1F | P2RY2 | TEM5 |
| CELSR2 | FZD6 | GPR62 | HTR2A | P2RY6 | TM7SF1 |
| CELSR3 | FZD7 | GPR63 | HTR2B | P2Y5 | TM7SF1L1 |
| CHRM1 | GABBR1 | GPR64 | HTR2C | PGR1 | TM7SF1L2 |
| CHRM2 | GALR1 | GPR66 | HTR4 | PGR10 | TM7SF3 |
| CHRM3 | GALR2 | GPR7 | HTR5A | PGR11 | TPRA40 |
| CHRM4 | GIPR | GPR73L1 | HTR7 | PGR13 | TRHR |
| CHRM5 | GLP1R | GPR75 | HUMNP1Y20 | PGR14 | TRHR2 |
| CMKBR1L2 | GPCR150 | GPR77 | KIAA0758 | PGR15 | |
| CMKLR1 | GPR1 | GPR80 | KIAA1828 | PGR18 | |

Pituitary. GPCRs expressed in the pituitary are listed in Table 5. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the pituitary. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of disease, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 5. GPCRs Expressed in the Pituitary

| | | | | | |
|-----------|----------|---------|---------|----------|----------|
| ADCYAP1R1 | CMKLR1 | FZD4 | GPR6 | KIAA0758 | PGR28 |
| ADMR | CNR1 | FZD5 | GPR62 | KIAA1828 | PGR3 |
| ADORA1 | CNR2 | FZD6 | GPR63 | LEC1 | PGR4 |
| ADORA2A | CRHR1 | G2A | GPR65 | LEC2 | PGR7 |
| ADORA2B | CX3CR1 | GABBR1 | GPR66 | LEC3 | PGR8 |
| ADORA3 | CXCR4 | GALR1 | GPR68 | LGR6 | PTAFR |
| ADRB1 | CXCR6 | GALR3 | GPR7 | LHCGR | PTGDR |
| ADRB2 | CYSLT1 | GHRHR | GPR73 | LTB4R | PTGER2 |
| AGTR1 | CYSLT2 | GHSR | GPR73L1 | MAS1 | PTGER3 |
| AGTRL1 | DJ287G14 | GLP1R | GPR74 | MC1R | PTGER4 |
| AVPR1B | DRD1 | GNRHR | GPR75 | MC3R | PTGFR |
| BAI2 | DRD2 | GPCR150 | GPR81 | MC4R | RAI3 |
| BAI3 | DRD3 | GPR10 | GPR82 | MRG | RDC1 |
| BDKRB1 | DRD4 | GPR105 | GPR84 | MrgA1 | RE2 |
| BDKRB2 | EBI2 | GPR12 | GPR85 | MrgG | RHO |
| C3AR1 | EDG1 | GPR18 | GPR86 | NMU2R | SALPR |
| C5R1 | EDG2 | GPR19 | GPR87 | NTSR2 | SMOH |
| CALCRL | EDG3 | GPR20 | GPR9 | OPRL1 | SREB3 |
| CASR | EDG4 | GPR21 | GPR92 | OPRM1 | SSTR1 |
| CCKBR | EDG5 | GPR22 | GPRC5B | OXTR | SSTR2 |
| CCR1 | EDG6 | GPR23 | GPRC5C | P2RY1 | SSTR3 |
| CCR2 | EDNRA | GPR24 | GRCA | P2RY12 | SSTR4 |
| CCR4 | EDNRB | GPR27 | GRM5 | P2RY2 | SSTR5 |
| CCR5 | EMR1 | GPR30 | GRM6 | P2RY6 | TEM5 |
| CCR6 | ETL | GPR31 | GRPR | P2Y10 | TM7SF1 |
| CCR7 | F2R | GPR34 | H963 | P2Y5 | TM7SF1L1 |
| CCR8 | F2RL1 | GPR35 | HCRTR1 | PGR1 | TM7SF1L2 |
| CCRL1 | F2RL2 | GPR37L1 | HGPCR11 | PGR10 | TM7SF3 |
| CD97 | F2RL3 | GPR39 | HM74 | PGR12 | TPRA40 |

| | | | | | |
|----------|---------|-------|-------|-------|-------|
| CELSR1 | FKSG79 | GPR4 | HRH1 | PGR13 | TRHR |
| CELSR2 | FPR1 | GPR43 | HRH2 | PGR15 | TRHR2 |
| CELSR3 | FPR-RS2 | GPR45 | HRH3 | PGR16 | TSHR |
| CHRM1 | FSHR | GPR48 | HTR1D | PGR19 | VIPR2 |
| CHRM2 | FY | GPR49 | HTR1F | PGR21 | VLGR1 |
| CHRM3 | FZD1 | GPR50 | HTR2A | PGR22 | |
| CHRM4 | FZD10 | GPR51 | HTR2B | PGR25 | |
| CHRM5 | FZD2 | GPR54 | HTR4 | PGR26 | |
| CMKBR1L2 | FZD3 | GPR56 | IL8RA | PGR27 | |

Brain. GPCRs expressed in the female brain are listed in Table 6, and GPCRs expressed in the male brain are listed in Table 7. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the female or male nervous system. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the nervous system, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

10

Table 6. GPCRs Expressed in the Female Brain

| | | | | | |
|-----------|----------|---------|---------|----------|--------|
| ADCYAP1R1 | CNR2 | GIPR | GPR7 | KIAA0758 | PGR18 |
| ADMR | CRHR1 | GLP1R | GPR73 | KIAA1828 | PGR20 |
| ADORA1 | CRHR2 | GLP2R | GPR73L1 | LEC1 | PGR21 |
| ADORA2A | CX3CR1 | GPCR150 | GPR75 | LEC2 | PGR22 |
| ADORA2B | CXCR4 | GPR1 | GPR77 | LEC3 | PGR25 |
| ADORA3 | CXCR6 | GPR10 | GPR80 | LGR6 | PGR27 |
| ADRA1A | CYSLT1 | GPR101 | GPR81 | LGR7 | PGR28 |
| ADRA1D | DJ287G14 | GPR103 | GPR82 | LGR8 | PGR3 |
| ADRA2A | DRD1 | GPR105 | GPR83 | LTB4R2 | PGR5 |
| ADRA2B | DRD2 | GPR12 | GPR84 | MAS1 | PGR7 |
| ADRB1 | DRD3 | GPR14 | GPR85 | MC3R | PGR8 |
| ADRB2 | DRD4 | GPR15 | GPR86 | MC4R | PTAFR |
| AGR9 | DRD5 | GPR17 | GPR88 | MC5R | PTGDR |
| AGTR2 | EBI2 | GPR18 | GPR92 | MRG | PTGER1 |
| AGTRL1 | EDG1 | GPR19 | GPRC5B | MrgA1 | PTGER2 |
| AVPR2 | EDG2 | GPR20 | GPRC5C | MRGE | PTGER3 |

| | | | | | |
|--------|---------|---------|-----------|--------|----------|
| BAI1 | EDG3 | GPR21 | GPRC5D | MRGF | PTGER4 |
| BAI2 | EDG4 | GPR22 | GRCA | MrgG | PTGFR |
| BAI3 | EDG5 | GPR23 | GRM1 | MTNR1A | PTHR1 |
| BDKRB1 | EDG6 | GPR24 | GRM2 | NMBR | PTHR2 |
| BLR1 | EDG7 | GPR26 | GRM3 | NMU2R | RAI3 |
| BRS3 | EDG8 | GPR27 | GRM4 | NPFF1R | RDC1 |
| C3AR1 | EDNRA | GPR3 | GRM5 | NPY1R | RE2 |
| C5R1 | EDNRB | GPR30 | GRM6 | NPY5R | RRH |
| CALCR | EMR1 | GPR34 | GRM7 | NTSR1 | SCTR |
| CALCRL | ETL | GPR35 | GRM8 | NTSR2 | SMOH |
| CASR | F2R | GPR37 | GRPR | OA1 | SREB3 |
| CCBP2 | F2RL1 | GPR37L1 | H963 | OPN1MW | SSTR1 |
| CCKAR | F2RL2 | GPR4 | HCRTR1 | OPN1SW | SSTR2 |
| CCKBR | F2RL3 | GPR43 | HCRTR2 | OPN3 | SSTR3 |
| CCR1 | FKSG79 | GPR45 | HGPCR11 | OPRD1 | SSTR4 |
| CCR2 | FPR1 | GPR48 | HGPCR2 | OPRK1 | SSTR5 |
| CCR5 | FPR-RS2 | GPR49 | HRH1 | OPRL1 | TACR1 |
| CCR6 | FY | GPR50 | HRH2 | OPRM1 | TACR3 |
| CCR8 | FZD1 | GPR51 | HRH3 | OXTR | TBXA2R |
| CCRL1 | FZD10 | GPR54 | HTR1A | P2RY1 | TEM5 |
| CD97 | FZD2 | GPR55 | HTR1B | P2RY12 | TM7SF1 |
| CELSR1 | FZD3 | GPR56 | HTR1D | P2RY6 | TM7SF1L1 |
| CELSR2 | FZD4 | GPR57 | HTR1F | P2Y10 | TM7SF1L2 |
| CELSR3 | FZD5 | GPR6 | HTR2A | P2Y5 | TM7SF3 |
| CHRM1 | FZD6 | GPR61 | HTR2B | PGR1 | TPRA40 |
| CHRM2 | FZD7 | GPR62 | HTR2C | PGR10 | TRHR |
| CHRM3 | FZD8 | GPR63 | HTR4 | PGR11 | TRHR2 |
| CHRM4 | GABBR1 | GPR64 | HTR5A | PGR12 | TSHR |
| CHRM5 | GALR1 | GPR65 | HTR6 | PGR13 | VIPR1 |
| CMKLR1 | GALR2 | GPR66 | HTR7 | PGR14 | VIPR2 |
| CNR1 | GHSR | GPR68 | HUMNP1Y20 | PGR15 | VLGR1 |

Table 7. GPCRs Expressed in the Male Brain

| | | | | | |
|-----------|--------|--------|---------|-----------|-------|
| ADCYAP1R1 | CHRM4 | GABBR1 | GPR65 | HUMNP1Y20 | PGR17 |
| ADMR | CHRM5 | GALR1 | GPR66 | KIAA0758 | PGR18 |
| ADORA1 | CMKLR1 | GALR2 | GPR68 | KIAA1828 | PGR20 |
| ADORA2A | CNR1 | GCGR | GPR7 | LEC1 | PGR21 |
| ADORA2B | CRHR1 | GIPR | GPR73L1 | LEC2 | PGR22 |
| ADORA3 | CRHR2 | GLP1R | GPR75 | LEC3 | PGR25 |

| | | | | | |
|--------|----------|---------|--------|--------|----------|
| ADRA1A | CX3CR1 | GLP2R | GPR77 | LGR6 | PGR27 |
| ADRA1D | CXCR4 | GPCR150 | GPR80 | LGR7 | PGR28 |
| ADRA2A | CXCR6 | GPR1 | GPR81 | LGR8 | PGR3 |
| ADRA2B | CYSLT1 | GPR10 | GPR82 | LHCGR | PGR7 |
| ADRA2C | DJ287G14 | GPR101 | GPR83 | LTB4R | PGR8 |
| ADRB1 | DRD1 | GPR103 | GPR84 | MAS1 | PTAFR |
| ADRB2 | DRD2 | GPR105 | GPR85 | MC3R | PTGDR |
| AGR9 | DRD3 | GPR12 | GPR86 | MC4R | PTGER1 |
| AGTR1 | DRD4 | GPR14 | GPR88 | MC5R | PTGER3 |
| AGTR2 | DRD5 | GPR15 | GPR92 | MRG | PTGER4 |
| AGTRL1 | EBI2 | GPR17 | GPRC5B | MRGE | PTGFR |
| AVPR2 | EDG1 | GPR18 | GPRC5C | MRGF | PTHR1 |
| BAI1 | EDG2 | GPR19 | GPRC5D | MTNR1A | PTHR2 |
| BAI2 | EDG3 | GPR21 | GRCA | NMBR | RAI3 |
| BAI3 | EDG4 | GPR22 | GRM1 | NMU2R | RDC1 |
| BDKRB1 | EDG5 | GPR23 | GRM2 | NPFF1R | RE2 |
| BDKRB2 | EDG6 | GPR24 | GRM3 | NPY1R | RRH |
| BRS3 | EDG7 | GPR26 | GRM4 | NPY2R | SMOH |
| C3AR1 | EDG8 | GPR27 | GRM5 | NPY5R | SREB3 |
| C5R1 | EDNRA | GPR3 | GRM6 | NTSR1 | SSTR1 |
| CALCR | EDNRB | GPR30 | GRM7 | NTSR2 | SSTR2 |
| CALCRL | EMR1 | GPR34 | GRM8 | OA1 | SSTR3 |
| CASR | ETL | GPR35 | GRPR | OPN1MW | SSTR4 |
| CCBP2 | F2R | GPR37 | H963 | OPN3 | SSTR5 |
| CCKAR | F2RL1 | GPR37L1 | HCRT1R | OPRD1 | TACR1 |
| CCKBR | F2RL2 | GPR4 | HCRT2R | OPRK1 | TACR3 |
| CCR1 | F2RL3 | GPR43 | HRH1 | OPRL1 | TEM5 |
| CCR4 | FKSG79 | GPR44 | HRH2 | OPRM1 | TM7SF1 |
| CCR5 | FPR-RS2 | GPR45 | HRH3 | OXTR | TM7SF1L1 |
| CCR6 | FY | GPR48 | HTR1A | P2RY1 | TM7SF1L2 |
| CCR7 | FZD1 | GPR49 | HTR1B | P2RY12 | TM7SF3 |
| CCR8 | FZD10 | GPR50 | HTR1D | P2RY2 | TPRA40 |
| CCRL1 | FZD2 | GPR51 | HTR1F | P2RY6 | TRHR |
| CD97 | FZD3 | GPR54 | HTR2A | P2Y5 | TRHR2 |
| CELSR1 | FZD4 | GPR55 | HTR2B | PGR1 | TSHR |
| CELSR2 | FZD5 | GPR56 | HTR2C | PGR10 | VIPR2 |
| CELSR3 | FZD6 | GPR6 | HTR4 | PGR11 | VLGR1 |
| CHRM1 | FZD7 | GPR61 | HTR5A | PGR13 | |
| CHRM2 | FZD8 | GPR62 | HTR6 | PGR14 | |
| CHRM3 | G2A | GPR63 | HTR7 | PGR15 | |

Brainstem and midbrain. GPCRs expressed in the brainstem and midbrain are listed in Table 8. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the nervous system. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the nervous system, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 8. GPCRs Expressed in the Brainstem

| | | | | | |
|-----------|----------|---------|---------|-----------|--------|
| ADCYAP1R1 | CMKBR1L2 | GALR2 | GPR66 | HTR4 | PGR15 |
| ADMR | CMKLR1 | GHSR | GPR68 | HTR5A | PGR16 |
| ADORA1 | CNR1 | GIPR | GPR7 | HTR6 | PGR18 |
| ADORA2A | CNR2 | GLP1R | GPR73 | HTR7 | PGR20 |
| ADORA2B | CRHR1 | GPCR150 | GPR73L1 | HUMNP1Y20 | PGR21 |
| ADORA3 | CRHR2 | GPR1 | GPR74 | KIAA0758 | PGR22 |
| ADRA1A | CX3CR1 | GPR10 | GPR75 | KIAA1828 | PGR23 |
| ADRA1D | CXCR4 | GPR101 | GPR77 | LEC1 | PGR27 |
| ADRA2A | CXCR6 | GPR103 | GPR80 | LEC2 | PGR28 |
| ADRA2B | CYSLT1 | GPR105 | GPR81 | LEC3 | PGR3 |
| ADRB1 | DJ287G14 | GPR12 | GPR82 | LGR6 | PGR7 |
| ADRB2 | DRD1 | GPR14 | GPR83 | LGR8 | PPYR1 |
| AGR9 | DRD2 | GPR15 | GPR84 | LHCGR | PTAFR |
| AGTR1 | DRD3 | GPR17 | GPR85 | MAS1 | PTGDR |
| AGTR2 | DRD5 | GPR18 | GPR86 | MC2R | PTGER1 |
| AGTRL1 | EBI2 | GPR19 | GPR87 | MC3R | PTGER2 |
| AVPR1A | EDG1 | GPR2 | GPR88 | MC4R | PTGER3 |
| AVPR2 | EDG2 | GPR20 | GPR90 | MC5R | PTGER4 |
| BAI1 | EDG3 | GPR21 | GPR92 | MRG | PTGFR |
| BAI2 | EDG4 | GPR22 | GPRC5B | MRGE | PTGIR |
| BAI3 | EDG5 | GPR23 | GPRC5C | MRGF | RAI3 |
| BDKRB1 | EDG6 | GPR24 | GPRC5D | MTNR1A | RDC1 |
| BDKRB2 | EDG7 | GPR26 | GRCA | NMBR | RE2 |
| BLR1 | EDG8 | GPR27 | GRM1 | NMU2R | RRH |
| BRS3 | EDNRA | GPR3 | GRM2 | NPFF1R | SALPR |
| C5R1 | EDNRB | GPR30 | GRM3 | NPY2R | SCTR |
| CALCR | EMR1 | GPR31 | GRM4 | NPY5R | SMOH |
| CALCRL | ETL | GPR34 | GRM5 | NTSR1 | SREB3 |
| CASR | F2R | GPR35 | GRM7 | NTSR2 | SSTR1 |
| CCBP2 | F2RL1 | GPR37 | GRM8 | OA1 | SSTR2 |
| CCKAR | F2RL2 | GPR37L1 | GRPR | OPN1MW | SSTR3 |
| CCKBR | FKSG79 | GPR4 | H963 | OPN3 | SSTR4 |
| CCR1 | FPR1 | GPR41 | HCRTR1 | OPRD1 | TACR2 |
| CCR5 | FPR-RS2 | GPR43 | HCRTR2 | OPRK1 | TACR3 |

| | | | | | |
|--------|--------|-------|---------|--------|----------|
| CCR6 | FY | GPR45 | HGPCR11 | OPRL1 | TEM5 |
| CCR7 | FZD1 | GPR48 | HGPCR2 | OPRM1 | TM7SF1 |
| CCRL1 | FZD10 | GPR49 | HRH1 | OXTR | TM7SF1L1 |
| CD97 | FZD2 | GPR50 | HRH2 | P2RY1 | TM7SF1L2 |
| CELSR1 | FZD3 | GPR51 | HRH3 | P2RY12 | TM7SF3 |
| CELSR2 | FZD4 | GPR54 | HTR1A | P2RY2 | TPRA40 |
| CELSR3 | FZD5 | GPR56 | HTR1B | P2RY6 | TRHR |
| CHRM1 | FZD6 | GPR6 | HTR1D | P2Y5 | TRHR2 |
| CHRM2 | FZD7 | GPR61 | HTR1F | PGR10 | TSHR |
| CHRM3 | G2A | GPR62 | HTR2A | PGR11 | VIPR2 |
| CHRM4 | GABBR1 | GPR63 | HTR2B | PGR13 | VLGR1 |
| CHRM5 | GALR1 | GPR65 | HTR2C | PGR14 | |

Cerebellum. GPCRs expressed in the cerebellum are listed in Table 9. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the cerebellum. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of disease, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

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Table 9. GPCRs Expressed in the Cerebellum

| | | | | | |
|-----------|----------|---------|--------|--------|--------|
| ADCYAP1R1 | CNR1 | GALR1 | GPR75 | LEC1 | PGR22 |
| ADMR | CNR2 | GALR2 | GPR77 | LEC2 | PGR23 |
| ADORA1 | CRHR1 | GALR3 | GPR80 | LEC3 | PGR26 |
| ADORA2A | CRHR2 | GCGR | GPR81 | LGR6 | PGR27 |
| ADORA2B | CX3CR1 | GIPR | GPR82 | LGR7 | PGR28 |
| ADORA3 | CXCR4 | GLP1R | GPR83 | LHCGR | PGR3 |
| ADRA1A | CXCR6 | GLP2R | GPR84 | LTB4R | PGR4 |
| ADRA1D | CYSLT1 | GPCR150 | GPR85 | LTB4R2 | PGR7 |
| ADRA2A | CYSLT2 | GPR1 | GPR86 | MAS1 | PGR8 |
| ADRA2B | DJ287G14 | GPR10 | GPR87 | MC3R | PTAFR |
| ADRB1 | DRD2 | GPR105 | GPR90 | MC4R | PTGDR |
| ADRB2 | DRD3 | GPR12 | GPR92 | MC5R | PTGER1 |
| AGR9 | DRD4 | GPR14 | GPRC5B | MRG | PTGER2 |
| AGTR1 | DRD5 | GPR15 | GPRC5C | MRGE | PTGER3 |
| AGTR2 | EBI2 | GPR17 | GRCA | MRGF | PTGER4 |
| AGTRL1 | EDG1 | GPR18 | GRM1 | MrgG | PTGFR |
| AVPR2 | EDG2 | GPR19 | GRM2 | NMBR | PTGIR |
| BAI1 | EDG3 | GPR2 | GRM3 | NPY5R | PTHR1 |
| BAI2 | EDG4 | GPR21 | GRM4 | NPY6R | PTHR2 |
| BAI3 | EDG5 | GPR22 | GRM5 | NTSR1 | RAI3 |
| BDKRB1 | EDG7 | GPR23 | GRM7 | NTSR2 | RDC1 |

| | | | | | |
|--------|---------|---------|------------|--------|----------|
| BLR1 | EDG8 | GPR24 | GRM8 | OA1 | RE2 |
| C3AR1 | EDNRA | GPR26 | H963 | OPN3 | RHO |
| C5R1 | EDNRB | GPR27 | HCRT1 | OPRD1 | RRH |
| CALCR | EMR1 | GPR30 | HCRT2 | OPRL1 | SCTR |
| CALCRL | ETL | GPR34 | HGPCR11 | OPRM1 | SMOH |
| CCKBR | F2R | GPR35 | HGPCR19 | OXTR | SREB3 |
| CCR1 | F2RL1 | GPR37 | HM74 | P2RY1 | SSTR1 |
| CCR5 | F2RL2 | GPR37L1 | HRH1 | P2RY12 | SSTR2 |
| CCR6 | F2RL3 | GPR4 | HRH2 | P2RY2 | SSTR3 |
| CCR7 | FPR1 | GPR43 | HRH3 | P2RY4 | SSTR4 |
| CCR8 | FPR-RS2 | GPR44 | HTR1A | P2RY6 | SSTR5 |
| CCR9 | FY | GPR45 | HTR1B | P2Y10 | TAR1 |
| CCRL1 | FZD1 | GPR48 | HTR1F | P2Y5 | TBXA2R |
| CD97 | FZD10 | GPR49 | HTR2A | PGR1 | TEM5 |
| CELSR1 | FZD2 | GPR50 | HTR2B | PGR11 | TM7SF1 |
| CELSR2 | FZD3 | GPR51 | HTR2C | PGR12 | TM7SF1L1 |
| CELSR3 | FZD4 | GPR54 | HTR4 | PGR13 | TM7SF1L2 |
| CHRM1 | FZD5 | GPR55 | HTR5A | PGR14 | TM7SF3 |
| CHRM2 | FZD6 | GPR62 | HTR7 | PGR15 | TPRA40 |
| CHRM3 | FZD7 | GPR63 | HUMNPIIY20 | PGR16 | TRHR2 |
| CHRM4 | FZD8 | GPR66 | IL8RA | PGR18 | TSHR |
| CHRM5 | G2A | GPR68 | KIAA0758 | PGR20 | VIPR2 |
| CMKLR1 | GABBR1 | GPR73L1 | KIAA1828 | PGR21 | |

Cerebral cortex. GPCRs expressed in the regions of the cerebral cortex other than the frontal cortex are listed in Table 10. These receptors are thus potential targets for therapeutic compounds that may modulate GPCR activity, expression, or stability in the cerebral cortex. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder involving the cerebral cortex, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

10

Table 10. GPCRs Expressed in the Cortex

| | | | | | |
|-----------|--------|---------|---------|------------|-------|
| ADCYAP1R1 | CMKLR1 | GALR2 | GPR68 | HTR7 | PGR20 |
| ADMR | CNR1 | GCGR | GPR7 | HUMNPIIY20 | PGR21 |
| ADORA1 | CNR2 | GHSR | GPR73 | IL8RA | PGR22 |
| ADORA2A | CRHR1 | GLP1R | GPR73L1 | KIAA0758 | PGR25 |
| ADORA2B | CRHR2 | GLP2R | GPR74 | KIAA1828 | PGR26 |
| ADORA3 | CX3CR1 | GPCR150 | GPR75 | LEC1 | PGR28 |
| ADORA1A | CXCR4 | GPR1 | GPR77 | LEC2 | PGR3 |
| ADORA1D | CXCR6 | GPR10 | GPR80 | LEC3 | PGR7 |

| | | | | | |
|----------|----------|---------|--------|--------|----------|
| ADRA2A | CYSLT1 | GPR101 | GPR81 | LGR6 | PGR8 |
| ADRA2B | CYSLT2 | GPR103 | GPR82 | LGR7 | PTAFR |
| ADRA2C | DJ287G14 | GPR105 | GPR83 | LGR8 | PTGDR |
| ADRB1 | DRD1 | GPR12 | GPR84 | LHCGR | PTGER1 |
| ADRB2 | DRD2 | GPR14 | GPR85 | LTB4R | PTGER3 |
| AGR9 | DRD3 | GPR17 | GPR86 | MAS1 | PTGER4 |
| AGTR1 | DRD5 | GPR18 | GPR87 | MC1R | PTGFR |
| AGTRL1 | EBI2 | GPR19 | GPR88 | MC3R | PTHR1 |
| AVPR2 | EDG1 | GPR20 | GPR92 | MC4R | PTHR2 |
| BAI1 | EDG2 | GPR21 | GPRC5B | MC5R | RAI3 |
| BAI2 | EDG3 | GPR22 | GPRC5C | MRG | RDC1 |
| BAI3 | EDG4 | GPR23 | GPRC5D | MRGE | RE2 |
| BDKRB2 | EDG5 | GPR24 | GRCA | MRGF | SALPR |
| C3AR1 | EDG7 | GPR26 | GRM1 | NMBR | SCTR |
| C5R1 | EDG8 | GPR27 | GRM2 | NPY1R | SMOH |
| CALCR | EDNRA | GPR3 | GRM3 | NPY5R | SREB3 |
| CALCRL | EDNRB | GPR30 | GRM4 | NTSR1 | SSTR1 |
| CASR | EMR1 | GPR31 | GRM5 | NTSR2 | SSTR2 |
| CCBP2 | ETL | GPR34 | GRM7 | OPN1MW | SSTR3 |
| CCKBR | F2R | GPR35 | GRM8 | OPN3 | SSTR4 |
| CCR1 | F2RL1 | GPR37 | GRPR | OPRD1 | SSTR5 |
| CCR2 | F2RL2 | GPR37L1 | H963 | OPRK1 | TACR3 |
| CCR5 | F2RL3 | GPR4 | HCRT1 | OPRL1 | TBXA2R |
| CCR6 | FPR1 | GPR41 | HCRT2 | OPRM1 | TEM5 |
| CCR7 | FPR-RS2 | GPR43 | HM74 | OXTR | TM7SF1 |
| CCR9 | FY | GPR44 | HRH1 | P2RY1 | TM7SF1L1 |
| CCRL1 | FZD1 | GPR45 | HRH2 | P2RY12 | TM7SF1L2 |
| CCXCR1 | FZD10 | GPR48 | HRH3 | P2RY6 | TM7SF3 |
| CD97 | FZD2 | GPR50 | HTR1A | P2Y10 | TPRA40 |
| CELSR1 | FZD3 | GPR51 | HTR1B | P2Y5 | TRHR |
| CELSR2 | FZD4 | GPR54 | HTR1D | PGR1 | TRHR2 |
| CELSR3 | FZD5 | GPR55 | HTR1F | PGR10 | TSHR |
| CHRM1 | FZD6 | GPR56 | HTR2A | PGR11 | VIPR1 |
| CHRM2 | FZD7 | GPR6 | HTR2B | PGR13 | VIPR2 |
| CHRM3 | FZD8 | GPR61 | HTR2C | PGR14 | VLGR1 |
| CHRM4 | G2A | GPR62 | HTR4 | PGR15 | |
| CHRM5 | GABBR1 | GPR63 | HTR5A | PGR16 | |
| CMKBR1L2 | GALR1 | GPR66 | HTR6 | PGR18 | |

- Frontal cortex.* GPCRs expressed in the frontal cortex are listed in Table 11. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the frontal cortex. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder involving the frontal cortex, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 11. GPCRs Expressed in the Frontal Cortex

| | | | | | |
|-----------|----------|---------|-----------|--------|----------|
| ADCYAP1R1 | CNR1 | GHRHR | GPR74 | LEC2 | PGR22 |
| ADMR | CNR2 | GIPR | GPR75 | LEC3 | PGR25 |
| ADORA1 | CRHR1 | GLP1R | GPR77 | LGR6 | PGR26 |
| ADORA2A | CRHR2 | GLP2R | GPR80 | LGR7 | PGR28 |
| ADORA2B | CX3CR1 | GPCR150 | GPR81 | LGR8 | PGR3 |
| ADORA3 | CXCR4 | GPR1 | GPR82 | LHCGR | PGR4 |
| ADRA1A | CXCR6 | GPR10 | GPR83 | LTB4R | PGR7 |
| ADRA1D | CYSLT1 | GPR101 | GPR84 | MAS1 | PPYR1 |
| ADRA2A | DJ287G14 | GPR103 | GPR85 | MC2R | PTAFR |
| ADRA2B | DRD1 | GPR105 | GPR86 | MC3R | PTGDR |
| ADRA2C | DRD2 | GPR12 | GPR87 | MC4R | PTGER1 |
| ADRB1 | DRD3 | GPR14 | GPR88 | MC5R | PTGER3 |
| ADRB2 | DRD4 | GPR15 | GPR92 | MRG | PTGER4 |
| AGR9 | DRD5 | GPR17 | GPRC5B | MRGE | PTGFR |
| AGTR1 | EBI2 | GPR18 | GPRC5D | MRGF | PTHR1 |
| AGTR2 | EDG1 | GPR19 | GRCA | NMBR | RAI3 |
| AGTRL1 | EDG2 | GPR2 | GRM1 | NMU2R | RDC1 |
| AVPR1A | EDG3 | GPR21 | GRM2 | NPY1R | RE2 |
| BAI1 | EDG5 | GPR22 | GRM3 | NPY2R | RHO |
| BAI2 | EDG7 | GPR23 | GRM4 | NPY5R | RRH |
| BAI3 | EDG8 | GPR24 | GRM5 | NTSR1 | SCTR |
| BDKRB1 | EDNRA | GPR26 | GRM7 | NTSR2 | SMOH |
| BDKRB2 | EDNRB | GPR27 | GRM8 | OA1 | SREB3 |
| C3AR1 | EMR1 | GPR3 | GRPR | OPN1MW | SSTR1 |
| C5R1 | ETL | GPR30 | H963 | OPN3 | SSTR2 |
| CALCRL | F2R | GPR34 | HCRTR1 | OPRD1 | SSTR3 |
| CASR | F2RL1 | GPR35 | HCRTR2 | OPRK1 | SSTR4 |
| CCBP2 | F2RL2 | GPR37 | HM74 | OPRL1 | SSTR5 |
| CCKAR | F2RL3 | GPR37L1 | HRH1 | OPRM1 | TACR1 |
| CCKBR | FPR1 | GPR4 | HRH2 | OXTR | TACR3 |
| CCR1 | FPR-RS2 | GPR43 | HRH3 | P2RY1 | TAR2 |
| CCR2 | FSHR | GPR45 | HTR1A | P2RY12 | TAR3 |
| CCR5 | FY | GPR48 | HTR1B | P2RY2 | TEM5 |
| CCR6 | FZD1 | GPR49 | HTR1D | P2RY6 | TM7SF1 |
| CCR7 | FZD10 | GPR50 | HTR1F | P2Y10 | TM7SF1L1 |
| CCRL1 | FZD2 | GPR54 | HTR2A | P2Y5 | TM7SF1L2 |
| CD97 | FZD3 | GPR55 | HTR2B | PGR10 | TM7SF3 |
| CELSR1 | FZD4 | GPR56 | HTR2C | PGR11 | TPRA40 |
| CELSR2 | FZD5 | GPR6 | HTR4 | PGR12 | TRHR |
| CELSR3 | FZD6 | GPR62 | HTR5A | PGR13 | TRHR2 |
| CHRM1 | FZD9 | GPR63 | HTR6 | PGR14 | TSHR |
| CHRM2 | G2A | GPR65 | HTR7 | PGR15 | VIPR1 |
| CHRM3 | GABBR1 | GPR66 | HUMNP1Y20 | PGR16 | VIPR2 |
| CHRM4 | GALR1 | GPR68 | KIAA0758 | PGR18 | VLGR1 |
| CHRM5 | GALR2 | GPR7 | KIAA1828 | PGR20 | |
| CMKLR1 | GALR3 | GPR73L1 | LEC1 | PGR21 | |

Hippocampus. GPCRs expressed in the hippocampus are listed in Table 12. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the hippocampus. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the hippocampus, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

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Table 12. GPCRs Expressed in the Hippocampus

| | | | | | |
|-----------|----------|---------|---------|------------|----------|
| ADCYAP1R1 | CNR1 | GALR3 | GPR65 | HTR2C | PGR16 |
| ADMR | CRHR1 | GHSR | GPR68 | HTR4 | PGR18 |
| ADORA1 | CRHR2 | GIPR | GPR7 | HTR5A | PGR20 |
| ADORA2A | CX3CR1 | GLP1R | GPR73L1 | HTR7 | PGR21 |
| ADORA2B | CXCR4 | GLP2R | GPR75 | HUMNP1IY20 | PGR22 |
| ADORA3 | CXCR6 | GPCR150 | GPR77 | KIAA0758 | PGR25 |
| ADRA1A | CYSLT1 | GPR1 | GPR80 | KIAA1828 | PGR27 |
| ADRA1D | DJ287G14 | GPR101 | GPR81 | LEC1 | PGR28 |
| ADRA2A | DRD1 | GPR103 | GPR82 | LEC2 | PGR3 |
| ADRA2B | DRD2 | GPR105 | GPR83 | LEC3 | PGR7 |
| ADRB1 | DRD5 | GPR12 | GPR84 | LGR6 | PTAFR |
| ADRB2 | EBI2 | GPR14 | GPR85 | LGR7 | PTGER1 |
| AGR9 | EDG1 | GPR15 | GPR86 | MAS1 | PTGER3 |
| AGTR1 | EDG2 | GPR17 | GPR87 | MC3R | PTHR1 |
| AGTR2 | EDG3 | GPR18 | GPR88 | MC4R | RDC1 |
| AVPR2 | EDG4 | GPR19 | GPR92 | MC5R | RE2 |
| BAI1 | EDG5 | GPR2 | GPRC5B | MRG | RRH |
| BAI2 | EDG6 | GPR21 | GPRC5C | MRGE | SALPR |
| BAI3 | EDG7 | GPR22 | GRCA | MRGF | SCTR |
| BDKRB1 | EDG8 | GPR23 | GRM1 | NMBR | SMOH |
| C3AR1 | EDNRA | GPR24 | GRM2 | NMU2R | SREB3 |
| CALCRL | EDNRB | GPR26 | GRM3 | NPFF1R | SSTR1 |
| CASR | EMR1 | GPR27 | GRM4 | NPY2R | SSTR2 |
| CCKAR | ETL | GPR3 | GRM5 | NTSR1 | SSTR3 |
| CCKBR | F2R | GPR30 | GRM7 | NTSR2 | SSTR4 |
| CCR2 | F2RL1 | GPR34 | GRM8 | OA1 | SSTR5 |
| CCR5 | F2RL2 | GPR37 | GRPR | OPN3 | TBXA2R |
| CCR6 | F2RL3 | GPR37L1 | H963 | OPRD1 | TEM5 |
| CCRL1 | FY | GPR4 | HCRT1 | OPRK1 | TM7SF1 |
| CCXCR1 | FZD1 | GPR44 | HCRT2 | OPRL1 | TM7SF1L1 |
| CD97 | FZD2 | GPR45 | HGPCR2 | OPRM1 | TM7SF1L2 |
| CELSR1 | FZD3 | GPR48 | HM74 | OXTR | TM7SF3 |
| CELSR2 | FZD4 | GPR49 | HRH1 | P2RY1 | TPRA40 |

| | | | | | |
|--------|--------|-------|-------|--------|-------|
| CELSR3 | FZD5 | GPR50 | HRH2 | P2RY12 | TRHR |
| CHRM1 | FZD6 | GPR51 | HRH3 | P2RY6 | TRHR2 |
| CHRM2 | FZD8 | GPR54 | HTR1A | P2Y5 | VIPR2 |
| CHRM3 | G2A | GPR55 | HTR1B | PGR10 | VLGR1 |
| CHRM4 | GABBR1 | GPR6 | HTR1F | PGR13 | |
| CHRM5 | GALR1 | GPR62 | HTR2A | PGR14 | |
| CMKLR1 | GALR2 | GPR63 | HTR2B | PGR15 | |

5 *Striatum.* GPCRs expressed in the striatum are listed in Table 13. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the striatum. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the striatum, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

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Table 13. GPCRs Expressed in the Striatum

| | | | | | |
|-----------|----------|---------|--------|--------|--------|
| ADCYAP1R1 | CNR1 | GLP1R | GPR74 | LEC1 | PGR22 |
| ADMR | CNR2 | GLP2R | GPR75 | LEC2 | PGR25 |
| ADORA1 | CRHR1 | GPCR150 | GPR77 | LEC3 | PGR26 |
| ADORA2A | CRHR2 | GPR1 | GPR80 | LGR6 | PGR27 |
| ADORA2B | CX3CR1 | GPR10 | GPR81 | LGR7 | PGR28 |
| ADORA3 | CXCR4 | GPR101 | GPR82 | LGR8 | PGR3 |
| ADRA1A | CXCR6 | GPR103 | GPR83 | LHCGR | PGR5 |
| ADRA1D | CYSLT1 | GPR105 | GPR84 | LTB4R | PGR7 |
| ADRA2A | CYSLT2 | GPR12 | GPR85 | LTB4R2 | PGR8 |
| ADRA2C | DJ287G14 | GPR14 | GPR86 | MAS1 | PTAFR |
| ADRB1 | DRD1 | GPR15 | GPR87 | MC2R | PTGDR |
| ADRB2 | DRD2 | GPR17 | GPR88 | MC3R | PTGER1 |
| ADRB3 | DRD3 | GPR18 | GPR9 | MC4R | PTGER2 |
| AGR9 | DRD4 | GPR19 | GPR90 | MC5R | PTGER3 |
| AGTR1 | DRD5 | GPR2 | GPR92 | MRG | PTGER4 |
| AGTR2 | EBI2 | GPR20 | GPRC5B | MrgA1 | PTGFR |
| AGTRL1 | EDG1 | GPR21 | GPRC5C | MRGE | PTGIR |
| AVPR1A | EDG2 | GPR22 | GPRC5D | MRGF | PTHR1 |
| AVPR1B | EDG3 | GPR23 | GRCA | MTNR1A | RDC1 |
| AVPR2 | EDG4 | GPR24 | GRM1 | NMBR | RE2 |
| BAI1 | EDG5 | GPR26 | GRM2 | NMU2R | RHO |
| BAI2 | EDG6 | GPR27 | GRM3 | NPFF1R | RRH |
| BAI3 | EDG7 | GPR3 | GRM4 | NPY1R | SALPR |
| BDKRB1 | EDG8 | GPR30 | GRM5 | NPY2R | SCTR |
| BLR1 | EDNRA | GPR31 | GRM7 | NPY5R | SMOH |
| BRS3 | EDNRB | GPR34 | GRM8 | NTSR1 | SREB3 |

| | | | | | |
|----------|---------|---------|-----------|--------|----------|
| C3AR1 | EMR1 | GPR35 | GRPR | NTSR2 | SSTR1 |
| C5R1 | ETL | GPR37 | H963 | OA1 | SSTR2 |
| CALCR | F2R | GPR37L1 | HCRT1 | OPN1MW | SSTR3 |
| CALCRL | F2RL1 | GPR4 | HCRT2 | OPN3 | SSTR4 |
| CCBP2 | F2RL2 | GPR41 | HGPCR11 | OPRD1 | SSTR5 |
| CCKAR | FKSG79 | GPR43 | HGPCR2 | OPRK1 | TACR1 |
| CCKBR | FPR1 | GPR45 | HM74 | OPRL1 | TACR3 |
| CCR1 | FPR-RS2 | GPR48 | HRH1 | OPRM1 | TBXA2R |
| CCR2 | FY | GPR49 | HRH2 | OXTR | TEM5 |
| CCR5 | FZD1 | GPR50 | HRH3 | P2RY1 | TM7SF1 |
| CCR6 | FZD10 | GPR51 | HTR1A | P2RY12 | TM7SF1L1 |
| CCR7 | FZD2 | GPR54 | HTR1B | P2RY6 | TM7SF1L2 |
| CCR9 | FZD3 | GPR55 | HTR1D | P2Y10 | TM7SF3 |
| CCRL1 | FZD4 | GPR56 | HTR1F | P2Y5 | TPRA40 |
| CD97 | FZD5 | GPR57 | HTR2A | PGR1 | TRHR |
| CELSR1 | FZD6 | GPR6 | HTR2B | PGR10 | TRHR2 |
| CELSR2 | FZD8 | GPR61 | HTR2C | PGR11 | TSHR |
| CELSR3 | FZD9 | GPR62 | HTR4 | PGR12 | VIPR1 |
| CHRM1 | G2A | GPR63 | HTR5A | PGR13 | VIPR2 |
| CHRM2 | GABBR1 | GPR65 | HTR6 | PGR14 | VLGR1 |
| CHRM3 | GALR1 | GPR66 | HTR7 | PGR15 | |
| CHRM4 | GALR2 | GPR68 | HUMNP1Y20 | PGR17 | |
| CHRM5 | GALR3 | GPR7 | IL8RB | PGR2 | |
| CMKBR1L2 | GHSR | GPR73 | KIAA0758 | PGR20 | |
| CMKLR1 | GIPR | GPR73L1 | KIAA1828 | PGR21 | |

Thalamus. GPCRs expressed in the thalamus are listed in Table 14. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the thalamus. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the thalamus, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

10

Table 14. GPCRs Expressed in the Thalamus

| | | | | | |
|-----------|----------|---------|-------|--------|-------|
| ADCYAP1R1 | CRHR1 | GIPR | GPR75 | LEC3 | PGR2 |
| ADMR | CRHR2 | GLP1R | GPR77 | LGR6 | PGR20 |
| ADORA1 | CX3CR1 | GLP2R | GPR80 | LGR7 | PGR21 |
| ADORA2A | CXCR4 | GPCR150 | GPR81 | LGR8 | PGR22 |
| ADORA2B | CXCR6 | GPR1 | GPR82 | LHCGR | PGR25 |
| ADORA3 | CYSLT1 | GPR10 | GPR83 | LTB4R | PGR26 |
| ADRA1A | DJ287G14 | GPR101 | GPR84 | LTB4R2 | PGR27 |
| ADRA1D | DRD1 | GPR103 | GPR85 | MAS1 | PGR28 |

| | | | | | |
|----------|---------|---------|-----------|--------|----------|
| ADRA2A | DRD2 | GPR105 | GPR86 | MC3R | PGR3 |
| ADRA2B | DRD3 | GPR12 | GPR87 | MC4R | PGR7 |
| ADRA2C | DRD4 | GPR14 | GPR88 | MC5R | PTAFR |
| ADRB1 | DRD5 | GPR15 | GPR9 | MRG | PTGDR |
| ADRB2 | EBI2 | GPR17 | GPR92 | MrgA1 | PTGER1 |
| ADRB3 | EDG1 | GPR18 | GPRC5B | MRGE | PTGER2 |
| AGR9 | EDG2 | GPR19 | GPRC5C | MRGF | PTGER3 |
| AGTR1 | EDG3 | GPR2 | GPRC5D | MrgG | PTGER4 |
| AGTR2 | EDG4 | GPR21 | GRCA | MTNR1A | PTGFR |
| AGTRL1 | EDG5 | GPR22 | GRM1 | NMBR | PTGIR |
| AVPR1A | EDG6 | GPR23 | GRM2 | NMU2R | PTHR1 |
| AVPR2 | EDG7 | GPR24 | GRM3 | NPFF1R | RAI3 |
| BAI1 | EDG8 | GPR26 | GRM4 | NPY1R | RDC1 |
| BAI2 | EDNRA | GPR27 | GRM5 | NPY2R | RE2 |
| BAI3 | EDNRB | GPR3 | GRM7 | NPY5R | RRH |
| BDKRB1 | EMR1 | GPR30 | GRM8 | NTSR1 | SCTR |
| BDKRB2 | ETL | GPR31 | GRPR | NTSR2 | SMOH |
| BRS3 | F2R | GPR34 | H963 | OA1 | SREB3 |
| C3AR1 | F2RL1 | GPR35 | HCRT1 | OPN1MW | SSTR1 |
| C5R1 | F2RL2 | GPR37 | HCRT2 | OPN3 | SSTR2 |
| CALCR | F2RL3 | GPR37L1 | HGPCR2 | OPRD1 | SSTR3 |
| CALCRL | FKSG79 | GPR4 | HM74 | OPRK1 | SSTR4 |
| CASR | FPR1 | GPR43 | HRH1 | OPRL1 | SSTR5 |
| CCKAR | FPR-RS2 | GPR44 | HRH2 | OPRM1 | TACR1 |
| CCKBR | FSHR | GPR45 | HRH3 | OXTR | TACR3 |
| CCR4 | FY | GPR48 | HRH4 | P2RY1 | TBXA2R |
| CCR5 | FZD1 | GPR49 | HTR1A | P2RY12 | TEM5 |
| CCR6 | FZD10 | GPR50 | HTR1B | P2RY2 | TM7SF1 |
| CCR7 | FZD2 | GPR51 | HTR1D | P2RY4 | TM7SF1L1 |
| CCRL1 | FZD3 | GPR54 | HTR1F | P2RY6 | TM7SF1L2 |
| CD97 | FZD4 | GPR55 | HTR2A | P2Y10 | TM7SF3 |
| CELSR2 | FZD5 | GPR56 | HTR2B | P2Y5 | TPRA40 |
| CELSR3 | FZD6 | GPR6 | HTR2C | PGR1 | TRHR |
| CHRM1 | FZD8 | GPR62 | HTR4 | PGR10 | TRHR2 |
| CHRM2 | FZD9 | GPR63 | HTR5A | PGR11 | TSHR |
| CHRM3 | G2A | GPR64 | HTR7 | PGR12 | VIPR1 |
| CHRM4 | GABBR1 | GPR65 | HUMNP1Y20 | PGR13 | VIPR2 |
| CHRM5 | GALR1 | GPR66 | IL8RA | PGR14 | VLGR1 |
| CMKBR1L2 | GALR2 | GPR68 | KIAA0758 | PGR15 | |
| CMKLR1 | GALR3 | GPR7 | KIAA1828 | PGR16 | |
| CNR1 | GHRHR | GPR73L1 | LEC1 | PGR17 | |
| CNR2 | GHSR | GPR74 | LEC2 | PGR18 | |

Exemplary diseases and disorders of the nervous system include

- 5 abetalipoproteinemia, abnormal social behaviors, absence (petit mal) epilepsy, absence seizures, abulia, acalculia, acidophilic adenoma, acoustic neuroma, acquired aphasia, acquired aphasia with epilepsy (Landau-Kleffner syndrome) specific reading disorder,

acquired epileptic aphasia, acromegalic neuropathy, acromegaly, action myoclonus-renal
 insufficiency syndrome, acute autonomic neuropathy, acute cerebellar ataxia in children,
 acute depression, acute disseminated encephalomyelitis, acute idiopathic sensory
 neuronopathy, acute intermittent porphyria, acute mania, acute mixed episode, acute
 5 pandysautonomia, acute polymorphic disorder with symptoms of schizophrenia, acute
 polymorphic psychotic disorder without symptoms of schizophrenia, acute purulent
 meningitis, addiction, Addison syndrome, adenovirus serotypes, adjustment disorders,
 adrenal hyperfunction, adrenal hypofunction, adrenoleukodystrophy,
 adrenomyeloneuropathy, advanced sleep-phase syndrome, affective disorder syndromes,
 10 agenesis of the corpus callosum, agnosia, agoraphobia, agraphia, agyria, agyria-pachygyria,
 ahylognosia, Aicardi syndrome, AIDS, akathisia, akinesia, akinetic mutism, akinetopsia,
 alcohol abuse, alcohol dependence syndrome, alcohol neuropathy, alcohol related disorders,
 alcoholic amblyopia, alcoholic blacknack oututs, alcoholic cerebellar degeneration,
 alcoholic dementia, alcoholic hallucinosis, alcoholic polyneuropathy, alcohol-induced
 15 anxiety disorders, alcohol-induced dementia, alcohol-induced mood disorders, alcohol-
 induced psychosis, alcoholism, Alexander's syndrome, alexia, alexia with agrphia, alexia
 without agraphia, alien hand syndrome, Alper's disease, altered sexuality syndromes,
 alternating hemiplegia, Alzheimer's disease, Alzheimer-like senile dementia, Alzheimer-
 like juvenile dementia, amenorrhea, aminoacidurias, amnesia, amnesia for offences, amok-
 20 type reactions, amorphognosia, amphetamine addiction, amphetamine or amphetamine-like
 related disorders, amphetamine withdrawal, amyloid neuropathy, amyotrophic lateral
 sclerosis, anencephaly, aneurysms, angioblastic meningiomas, Angleman's syndrome,
 anhidrosis, anisocoria, anomia, anomic aphasia, anorexia nervosa, anosmia, anosognosia,
 anterior cingulate syndrome, anterograde amnesia, antibiotic-induced neuromuscular
 25 blockade, antisocial personality disorder, Anton's syndrome, anxiety and obsessive-
 compulsive disorder syndromes, anxiety disorders, apathy syndromes, aphasia, aphemia,
 aplasia, apnea, apraxia, arachnoid cyst, archicerebellar syndrome, Arnold-Chiari
 malformation, arousal disorders, arrhinencephaly, arsenic poisoning, arteriosclerotic
 Parkinsonism, arteriovenous aneurysm, arteriovenous malformations, aseptic meningeal
 30 reaction, Asperger's syndrome, astereognosis, asthenia, astrocytomas, asymbolia, asynergia,

ataque de nervios, ataxia, ataxia telangiectasia, ataxic cerebral palsy, ataxic dysarthria, athetosis, atonia, atonic seizures, attention deficit disorder, attention-deficit and disruptive behavior disorders, attention-deficit hyperkinetic disorders, atypical Alzheimer's disease, atypical autism, autism, autism spectrum disorder, avoidant personality disorder, axial
 5 dementias, bacterial endocarditis, bacterial infections, Balint's syndrome, ballism, balo disease, basophilic adenoma, Bassen-Knock outznzweig syndrome, Batten disease, battered woman syndrome, Behçet syndrome, Bell' palsy, benign essential tremor, benign focal epilepsies of childhood, benign intracranial hypertension, benxodiazepine dependence, bilateral cortical dysfunction, Binswanger's disease, bipolar disorder, bipolar type 1
 10 disorder, bipolar type 2 disorder, blepharospasm, body dysmorphic disorder, Bogaert-Bertrand disease, Bogarad syndrome, borderline personality disorder, botulism, Bouffée Délirante-type reactions, brachial neuropathy, bradycardia, bradykinesia, brain abscess, brain edema, brain fog, brain stem glioma, brainstem encephalitis, brief psychotic disorder, broca's aphasia, brucellosis, bulimia, bulimia nervosa, butterfly glioma, cachexia, caffeine
 15 related disorders, california encephalitis, callosal agenesis, Canavan's syndrome, cancer pain, cannabis dependence, cannabis flashbacks, cannabis psychosis, cannabis related disorders, carcinoma-associated retinopathy, cardiac arrest, cavernous malformations, cellular (cytotoxic) edema, central facial paresis, central herniation syndrome, central neurogenic hyperventilation, central pontine myelinolysis, central post-stroke syndrome
 20 (thalamic pain syndrome), cerebellar hemorrhage, cerebellar tonsillar herniation syndrome, cerebral amyloid (congolophilic) angiopathy, cerebral hemorrhage, cerebral malaria, cerebral palsy, cerebral subdural empyema, cerebrotendinous xanthomatosis, cerebrovascular disorders, cervical tumors, cestodes, Charcot-Carrie-tooth disease, Chediak-Cigashi disease, Cheiro-oral syndrome, chiari malformation with hydrocephalus, childhood disintegrative
 25 disorder, childhood feeding problems, childhood sleep problems, cholesteatomas, chordomas, chorea, chorea gravidarum, choreoathetosis, chromophobe adenoma, chromosomal disorders, chronic biplar major depression, chronic bipolar disorder, chronic demyelinating polyneuritis, chronic depression, chronic fatigue syndrome, chronic gm2 gangliosidosis, chronic idiopathic sensory neuropathy, chronic inflammatory demyelinating
 30 polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, chronic pain,

chronic paroxysmal hemicrania, chronic sclerosing panencephalitis, chronic traumatic
 encephalopathy, chronobiological disorders, circadian rhythm disorder, circadian rhythm
 disorders, Claude's syndrome, clonic seizures, cluster headache, cocaine addiction, cocaine
 withdrawal, cocaine-related disorders, Cockayne's syndrome, colloid cysts of the third
 5 ventricle, colorado tick fever, coma, communicating hydrocephalus, communication
 disorders, complex partial seizures, compression neuropathy, compulsive buying disorder,
 conceptual apraxia, conduct disorders, conduction aphasia, conduction apraxia, congenital
 analgesia, congenital cytomegalovirus disease, congenital hydrocephalus, congenital
 hypothyroidism, congenital muscular dystrophy, congenital myasthenia, congenital
 10 myotonic dystrophy, congenital rubella syndrome, congophilic angiopathy, constipation,
 coprophilia, cornelia de lange syndrome, cortical dementias, cortical heteropias,
 corticobasal degeneration, corticobasal ganglionic degeneration, coxsackievirus, cranial
 meningoceles, craniopharyngioma, craniorachischisis, craniosynostosis, cranium bifidum,
 cretinism, Creutzfeldt-Jakob disease, Cri-du-Chat syndrome, cruciate hemiplegia,
 15 cryptococcal granulomas, cryptococcosis, culturally related syndromes, culturally
 stereotyped reactions to extreme environmental conditions (arctic hysteria), Cushing
 syndrome, cyclothymia, cysticercosis, cytomegalovirus, Dandy-Walker malformation,
 deafness, defects in the metabolism of amino acids, dehydration, Dejerine-Roussy
 syndrome, Dejerine-Sottas disease, delayed and advanced sleep phase syndromes, delayed
 20 ejaculation, delayed puberty, delayed-sleep-phase syndrome, delerium due to alcohol,
 delerium due to intoxication, delerium due to withdrawal, delirium, dementia, and amnesic
 and other cognitive disorders, delusional disorder, delusional disorder: erotomania subtype,
 delusional disorder: grandiose subtype, delusional disorder: jealousy subtype, delusional
 misidentification syndromes, dementia due to HIV disease, dementia pugilistica, dementias,
 25 dementias associated with extrapyramidal syndrome, dentatorubral-pallidoluysian atrophy,
 dependent personality disorder, depersonalization disorder, depression, depressive
 personality disorder, dermoids, developmental speech and language disorder, devic
 syndrome, devivo disease, diabetes, diabetes insipidus, diabetic neuropathy, dialysis
 demential, dialysis dysequilibrium syndrome, diencephalic dementias, diencephalic
 30 dysfunction, diencephalic syndrome of infancy, diencephalic vascular dementia, diffuse

- sclerosis, digestive disorders, diphtheria, diplopia, disarthria, disassociation apraxia, disorders of carbohydrate metabolism, disorders of excessive somnolence, disorders of metal metabolism, disorders of purine metabolism, disorders of sexual arousal, disorders of sexual aversion, disorders of sexual desire, disorders of the sleep-wake schedule,
- 5 dissociative disorders, dorsolateral tegmental pontine syndrome, Down syndrome, Down syndrome with dementia, drug dependance, drug overdose, drug-induced myasthenia, Duchenne muscular dystrophy, dwarfism, dysarthria, dysdiadochokinesia, dysembryoplastic neuroepithelial tumor, dysexecutive syndrome, dysgraphia, dyskinesia, dyskinetic cerebral palsy, dyslexia, dysmetria, dysomnia, dysosmia, dyspareunia, dysphagia, dysphasia,
- 10 dysphonia, dysplasia, dyspnea, dysprosody, dyssomnia, dyssynergia, dyesthesia, dysthymia, dystonia, dystrophinopathies, early adolescent gender identity disorder, early infantile epileptic encephalopathy (Ohtahara syndrome, early myoclonic epileptic encephalopathy, Eaton-Lambert syndrome, echinococcus (hydatid cysts), echolalia, echovirus, eclampsia, Edward's syndrome, elimination disorders, embolismintracerebral hemorrhage, Emery-
- 15 Dreifuss muscular dystrophy, encephalitis lethargica, encephaloceles, encephalotrigeminal angiomas, enophthalmos, enterovirus, enuresis, eosinophilic meningitis, ependymoma, epidural spinal cord compression, epilepsy, episodic ataxia, epstein-barr, equine encephalomyelitis, erectile dysfunction, essential thrombocythemia, essential tremor, esthesioneuroblastoma, excessive daytime somnolence, excessive secretion of antidiuretic
- 20 hormone, excessive sleepiness, exhibitionism, expressive language disorder, extramedullary tumors, extrasylvian aphasia, extratemporal neocortical epilepsy, fabry's disease, facioscapulohumeral muscular dystrophy, factitious disorder, factitious disorders, false memories, familial dysautonomia, familial periodic paralysis, familial spastic paraparesis, familial spastic paraplegias, fear disorders, feeding and eating disorders of infancy or early
- 25 childhood, female sexual arousal disorder, fetal alcohol syndrome, fetishism, flaccid dysarthria, floppy infant syndrome, focal inflammatory demyelinating lesions with mass effect, focal neonatal hypotonia, folie à deux, foramen magnum tumors, Foville's syndrome, fragile-x syndrome, Freidrich's ataxia, Frolich syndrome, frontal alexia, frontal convexity syndrome, frontotemporal dementia, frontotemporal dementias, frotteurism, fungal
- 30 infection, galactocerebroside lipidoses, galactorrhea, ganglioneuroma, Gaucher disease, gaze

palsy, gender identity disorder, generalized anxiety disorder, genital shrinking syndrome (Knock outro, Suo-Yang), germ cell tumors, Gerstmann's syndrome, Gerstmann-Straüssler syndrome, Gerstmann-Straussler-Schenker disease, Gertmann's syndrome, gestational substance abuse syndromes, giant axonal neuropathy, gigantism, Gilles de la Tourette syndrome, glioblastoma multiforme, gliomas, gliomatosis cerebri, global aphasia, 5 glossopharyngeal neuralgia, glycogen storage diseases, gm1-gangliosidosis, gm2-gangliosidoses, granular cell tumor, granulocytic brain edema, granulomas, granulomatous angiitis of the brain, Grave's disease, growild typeh hormone deficit , growild typeh-hormone secreting adenomas, guam-Parkinson complex dementia, Guillain-Barré syndrome, Hallervorden-Spatz disease, hallucinogen persisting perception disorder, 10 hallucinogen related disorders, hartnup disease, headache, helminthic infections (trichinellosis), hemangioblastomas, hemangiopericytomas, hemiachromatopsia, hemianesthesia, hemianopsia, hemiballism, hemiballismus, hemihypacusis, hemihypesthesia, hemiparesis, hemispatial neglect, hemophilus influenza meningitis, 15 hemorrhagic cerebrovascular disease, hepatic coma, hepatic encephalopathy, hepatolenticular degeneration (Wilson disease), hereditary amyloid neuropathy, hereditary ataxias, hereditary cerebellar ataxia, hereditary neuropathies, hereditary nonprogressive chorea, hereditary predisposition to pressure palsies, hereditary sensory autonomic neuropathy, hereditary sensory neuropathy, hereditary spastic paraplegia, hereditary 20 tyrosinemia, hermichorea, hermifacial spasm, herniation syndromes, herpes encephalitis, herpes infections, herpes zoster, herpes simplex, heterotopia, hexacarbon neuropathy, histrionic personality disorder, HIV, Holmes-Adie syndrome, homonymous quadrantanopsia, Horner's syndrome, human β -mannosidosis, Hunter's syndrome, Huntington's chorea, Huntington's disease, Hurler's syndrome, Hwa-Byung, hydraencephaly, hydrocephalus, 25 hyper thyroidism, hyperacusis, hyperalgesia, hyperammonemia, hypereosinophilic syndrome, hyperglycemia, hyperkalemic periodic paralysis, hyperkinesia, hyperkinesis, hyperkinetic dysarthria, hyperosmia, hyperosmolar hyperglycemic nonketonic diabetic coma, hyperparathyroidism, hyperphagia, hyperpituitarism, hyperprolactinemia, hypersexuality, hypersomnia, hypersomnia secondary to drug intake, hypersomnia-sleep- 30 apnea syndrome, hypersomnolence, hypertension, hypertensive encephalopathy,

- hyperthermia, hyperthyroidism (Graves disease), hypertonia, hypnagogic (predormital) hallucinations, hypnogenic paroxysmal dystonia, hypoadrenalism, hypoalgesia, hypochondriasis, hypoglycemia, hypoinsulinism, hypokalemic periodic paralysis, hypokinesia, hypokinetic dysarthria, hypomania, hypoparathyroidism, hypophagia,
- 5 hypopituitarism, hypoplasia, hyposmia, hyposthenuria, hypotension, hypothermia, hypothyroid neuropathy, hypothyroidism, hypotonia, Hyrler syndrome, hysteria, ideational apraxia, ideomotor apraxia, idiopathic hypersomnia, idiopathic intracranial hypertension, idiopathic orthostatic hypotension, immune mediated neuropathies, impersistence, impotence, impulse control disorders, impulse dyscontrol and aggression syndromes,
- 10 impulse-control disorders, incontinence, incontinentia pigmenti, infantile encephalopathy with cherry-red spots, infantile neuraxonal dystrophy, infantile spasms, infantilism, infarction, infertility, influenza, inhalant related disorders, insomnias, insufficient sleep syndrome, intention tremor, intermittent explosive disorder, internuclear ophthalmoplegia, interstitial (hydrocephalic) edema, intoxication, intracranial epidural abscess, intracranial
- 15 hemorrhage, intracranial hypotension, intracranial tumors, intracranial venous-sinus thrombosis, intradural hematoma, intramedullary tumors, intravascular lymphoma, ischemia, ischemic brain edema, ischemic cerebrovascular disease, ischemic neuropathies, isolated inflammatory demyelinating CNS syndromes, Jackson-Collet syndrome, Jaknock outb-Creutzfeld disease, Japanese encephalitis, jet lag syndrome, Joseph disease, Joubert's
- 20 syndrome, juvenile neuroaxonal dystrophy, Kayak-Svimmel, Kearns-Sayre syndrome, kinky hair disease (Menkes syndrome), Kleine-Levin syndrome, kleptomania, Klinefelter's syndrome, Kluver-Bucy syndrome, Knock outerber-Salus-Elschnig syndrome, Knock outksaknock outff's syndrome, krabbe disease, krabbe leuknock outdystrophy, Kugelberg-Welander syndrome, kuru, Lafora's disease, language deficits, language related disorders,
- 25 latah-type reactions, lateral mass herniation syndrome, lateropulsation, lathyrism, Laurence-Moon Biedl syndrome, Laurence-Moon syndrome, lead poisoning, learning disorders, leber hereditary optic atrophy, left ear extinction, legionella pneumophila infection, Leigh's disease, Lennoc-Gastaut syndrome, Lennox-Gastaut's syndrome, leprosy, leptospirosis, Lesch-Nyhan syndrome, leukemia, leuknock outdystrophies, Lévy-Roussy syndrome, lewy
- 30 body dementia, lewy body disease, limb girdle muscular dystrophies, limbic encephalitis,

- limbic encephalopathy, lissencephaly, localized hypertrophic neuropathy, locked-in syndrome, logoclonia, low pressure headache, Lowe syndrome, lumbar tumors, lupus anticoagulants, lyme disease, lyme neuropathy, lymphocytic choriomeningitis, lymphomas, lysosomal and other storage diseases, macroglobinemia, major depression with melancholia,
- 5 major depression with psychotic features, major depression without melancholia, major depressive (unipolar) disorder, male orgasmic disorder, malformations of septum pellucidum, malignant peripheral nerve sheath tumors, malingers, mania, mania with psychotic features, mania without psychotic features, maple syrup urine disease, Marchiafava-Bignami syndrome, Marcus Gunn syndrome, Marie-Foix syndrome,
- 10 Marinesco-Sjögren syndrome, Maroteaux-Lamy syndrome, masochism, masturbatory pain, measles, medial frontal syndrome, medial medullary syndrome, medial tegmental syndrome, medication-induced movement disorders, medullary dysfunction, medulloblastomas, medulloepithelioma, megalencephaly, melanocytic neoplasms, memory disorders, memory disturbances, meniere syndrome, meningeal carcinomatosis, meningeal
- 15 sarcoma, meningial gliomatosis, meningiomas, meningism, meningitis, meningococcal meningitis, mental neuropathy (the numb chin syndrome), mental retardation, mercury poisoning, metabolic neuropathies, metachromatic leukodystrophy, metastatic neuropathy, metastatic tumors, metazoal infections, microcephaly, microencephaly, micropolygyria, midbrain dysfunction, midline syndrome, migraine, mild depression,
- 20 Millard-Gubler syndrome, Miller-Dieker syndrome, minimal brain dysfunction syndrome, miosis, mitochondrial encephalopathy with lactic acidosis and stroke (melas), mixed disorders of scholastic skills, mixed dysarthrias, mixed transcortical aphasia, Möbius syndrome, Mollaret meningitis, monoclonal gammopathy, mononeuritis multiplex, monosymptomatic hypochondriacal psychosis, mood disorders, Moritz Benedikt syndrome,
- 25 Morquio syndrome, Morton's neuroma, motor neuron disease, motor neurone disease with dementia, motor neuropathy with multifocal conduction block, motor skills disorder, mucopolipidoses, mucopolysaccharide disorders, mucopolysaccharidoses, multifocal eosinophilic granuloma, multiple endocrine adenomatosis, multiple myeloma, multiple sclerosis, multiple system atrophy, multiple systems atrophy, multisystemic degeneration
- 30 with dementia, mumps, Munchausen syndrome, Munchausen syndrome by proxy, muscular

hypertonia, mutism, myasthenia gravis, mycoplasma pneumoniae infection, myoclonic seizures, myoclonic-astatic epilepsy (doose syndrome), myoclonus, myotonia congenita, myotonic dystrophy, myotonic muscular dystrophy, narcolepsy, narcissistic personality disorder, narcolepsy, narcolepsy-cataplexy syndrome, necrophilia, nectrotizing

5 encephalomyelopathy, Nelson's syndrome, neocerebellar syndrome, neonatal myasthenia, neonatal seizures, nervios, nerves, neurasthenia, neuroacanthocytosis, neuroaxonal dystrophy, neurocutaneous disorders, neurofibroma, neurofibromatosis, neurogenic orthostatic hypotension, neuroleptic malignant syndrome, neurologic complications of renal transplantation, neuromyelitis optica, neuromyotonia (Isaacs syndrome), neuronal ceroid

10 lipofuscinoses, neuro-ophthalmic disorders, neuropathic pain, neuropathies associated with infections, neuropathy associated with cryoglobulins, neuropathy associated with hepatic diseases, neuropathy induced by cold, neuropathy produced by chemicals, neuropathy produced by metals, neurosyphilis, new variant Creutzfeldt-Jaknock outb

15 disease, nicotine dependence, nicotine related disorders, nicotine withdrawal, niemann-pick disease, nocturnal dissociative disorders, nocturnal enuresis, nocturnal myoclonus, nocturnal sleep-related eating disorders, noecerebellar syndrome, non-alzheimer frontal-lobe degeneration, nonamyloid polyneuropathies associated with plasma cell dyscrasia, non-lethal suicidal behavior, nonlocalizing aphasic syndromes, normal pressure hydrocephalus, Nothnagel's syndrome, nystagmus, obesity, obsessive-compulsive (anankastic) personality

20 disorder, obsessive-compulsive disorder, obstetric factitious disorder, obstructive hydrocephalus, obstructive sleep apnea, obstructive sleep apnoea syndrome, obstructive sleep hypopnoea syndrome, occipital dementia, occlusive cerebrovascular disease, oculocerebrorenal syndrome of lowe, oculomotor nerve palsy, oculopharyngeal muscular dystrophy, oligodendrogliomas, olivopontocerebellar atrophy, ondine's curse, one and a half

25 syndrome, onychophagia, opiate dependance, opiate overdose, opiate withdrawal, opioid related disorders, oppositional defiant disorder, opsoclonus, orbitofrontal syndrome, orgasmic anhedonia, orgasmic disorders, osteosclerotic myeloma, other disorders of infancy, childhood, or adolescence, other medication-induced movement disorders, pachygyria, paedophilia, pain, pain syndromes, painful legs-moving toes syndrome,

30 paleocerebellar syndrome, palilalia, panhypopituitarism, panic disorder, panic disorders,

papillomas of the choroid plexus, paraganglioma, paragonimiasis, paralysis, paralysis
 agitans (shaking palsy), paramyotonia congenita, paraneoplastic cerebellar degeneration,
 paraneoplastic cerebellar syndrome, paraneoplastic neuropathy, paraneoplastic syndromes,
 paranoia, paranoid personality disorder, paranoid psychosis, paraphasia, paraphilias,
 5 paraphrenia, parasitic infections, parasomnia, parasomnia overlap disorder, parenchymatous
 cerebellar degeneration, paresis, paresthesia, parinaud's syndrome, Parkinson's disease,
 Parkinson-dementia complex of guam, Parkinsonism, Parkinsonism-plus syndromes,
 Parkinson's disease, paroxysmal ataxia, paroxysmal dyskinesia, partial (focal) seizures,
 partialism, passive-aggressive (negativistic) personality disorder, Patau's syndrome,
 10 pathological gambling, peduncular hallucinosis, Pelizaeus-Merzbacher disease,
 perineurioma, peripheral neuropathy, perisylvian syndromes, periventricular leuko-
 outmalacia, periventricular white matter disorder, periventricular-intraventricular
 hemorrhage, pernicious anemia, peroneal muscular atrophy, peroxisomal diseases,
 perseveration, persistence of cavum septi pellucidi, persistent vegetative state, personality
 15 disorders, pervasive developmental disorders, phencyclidine (or phencyclidine-like) related
 disorders, phencyclidine delirium, phencyclidine psychosis, phencyclidine-induced
 psychotic disorder, phenylketonuria, phobic anxiety disorder, phonic tics, photorecepto-
 degeneration, pibloktoq, Pick's disease, pineal cell tumors, pineoblastoma, pineocytoma,
 pituitary adenoma, pituitary apoplexy, pituitary carcinoma, pituitary dwarfism, placebo
 20 effect, Plummer's disease, pneumococcal meningitis, poikilothermia, polio, polycythemia
 vera, polydipsia, polyglucosan storage diseases, polymicrogyria, polymyositis,
 polyneuropathy with dietary deficiency states, polysubstance related disorder, polyuria,
 pontine dysfunction, pontosubicular neuronal necrosis, porencephaly, porphyric neuropathy,
 portal-systemic encephalopathy, postcoital headaches, postconcussion syndrome,
 25 postencephalic Parkinson syndrome, posthemorrhagic hydrocephalus, postinflammatory
 hydrocephalus, postpartum depression, postpartum psychoses, postpolio syndrome,
 postpsychotic depression, post-stroke hypersomnia, post-traumatic amnesia, post-traumatic
 epilepsy, post-traumatic hypersomnia, post-traumatic movement disorders, post-traumatic
 stress disorder, post-traumatic syndromes, Prader-Willi syndrome, precocious puberty,
 30 prefrontal dorsolateral syndrome, prefrontal lobe syndrome, premenstrual stress disorder,

premenstrual syndrome, primary amebic meningoencephalitis, primary CNS lymphoma,
 primary idiopathic thrombosis, primary lateral sclerosis, primitive neuroectodermal tumors,
 prion disease, problems related to abuse or neglect, progressive bulbar palsy, progressive
 frontal lobe dementias, progressive multifocal lueknock outencephalopathy, progressive
 5 muscular atrophy, progressive muscular dystrophies, progressive myoclonic epilepsies,
 progressive myoclonus epilepsies, progressive non-fluent aphasia, progressive partial
 epilepsies, progressive rubella encephalitis, progressive sclerosing poliodystrophy (Alpers
 disease), progressive subcortical gliosis, progressive supranuclear palsy, progressive
 supranuclear paralysis, progrssive external ophthalmoplegia, prolactinemia , prolactin-
 10 sectreting adenomas, prosopagnosia, protozoan infection, pseudobulbar palsy, pseudocyesis,
 pseudodementia, psychic blindness, psychogenic excoriation, psychogenic fugue,
 psychogenic pain syndromes, psychological mutism, psychosis after brain injury, psychotic
 syndromes, ptosis, public masturbation, puerperal panic, pulmonary edema, pure word
 deafness, pyromania, quadrantanopsia, rabies, radiation neuropathy, Ramsay Hunt
 15 syndrome, rape traume syndrome, rapid cycling disorder, rapid ejaculation, Raymond-
 Cestan-Chenais syndrome, receptive language disorder, recovered memories, recurrent
 bipolar episodes, recurrent brief dpression, recurrent hypersomnia, recurrent major
 depression, refsum disease, reiterative speech disturbances, relational problems, rem sleep
 behavior disorder, rem sleep behavioral disorder, repetitive self-mutilation, repressed
 20 memories, respiratory dysrhythmia, restless legs syndrome, Rett's syndrome, Reye
 syndrome, rhythmic movement disorders, rocky mountain spotted fever, rostral basal
 pontine syndrome, rubella, Rubinstein-Taybi syndrome, sadistic personality disorder, salla
 disease, Sandhoff disease, Sanfilippo syndrome, sarcoid neuropathy, sarcoidosis,
 scapuloperóneal syndromes, schistosomiasis (bilharziasis), schizencephaly, schizoaffective
 25 disorder, schizoid personality disorder, schizophrenia, schizophrenia and other psychotic
 disorders, schizophrenia-like psychosis, schizophreniform disorder, schizotypal personality
 disorder, school-refusal anxiety disorder, schwannoma, scrub typhus, seasonal depression,
 secondary spinal muscular atrophy, secondary thrombosis, sedative hypnotic or anxiolytic-
 related disorders, seizure disorders, selective mutism, self-defeating (masochistic)
 30 personality disorder, semen-loss syndrome (shen-k'uei, dhat, jiryan, sukra prameha), senile

chorea, senile dementia, sensory perineuritis, separation anxiety disorder, septal syndrome,
 septo-optic dysplasia, severe hypoxia, severe myoclonic epilepsy, sexual and gender
 identity disorders, sexual disorders, sexual dysfunctions, sexual pain disorders, sexual
 sadism, Shapiro syndrome, shift work sleep disorder, Shy-Drager syndrome, sialidosis,
 5 sialidosis type 1, sibling rivalry disorder, sickle cell anemia, Simmonds disease, simple
 partial seizures, simultanagnosia, sleep disorders, sleep paralysis, sleep terrors, sleep-related
 enuresis, sleep-related gastroesophageal reflux syndrome, sleep-related headaches, sleep-
 wake disorders, sleepwalking, Smith-Magenis syndrome, social anxiety disorder, social
 phobia, social relationship syndromes, somatoform disorders, somnambulism, Sotos
 10 syndrome, spasmodic dysphonia, spasmodic torticollis (wry neck), spastic cerebral palsy,
 spastic dysarthria, specific developmental disorder of motor function, specific
 developmental disorders of scholastic skills, specific developmental expressive language
 disorder, specific developmental receptive language disorder, specific disorders of
 arithmetical skills, specific phobia, specific speech articulation disorder, specific spelling
 15 disorder, speech impairment, spina bifida, spinal epidural abscess, spinal muscular atrophies,
 spinocerebellar ataxias, spirochete infections, spongiform encephalopathies, spongy
 degeneration of the nervous system, St. Louis encephalitis, stammer, staphylococcal
 meningitis, startle syndromes, status marmoratus, steele-richardson-olszewski syndrome,
 stereotypic movement disorder, stereotypies, stiff-man syndrome, stiff-person syndrome,
 20 stimulant psychosis, Strachan syndrome (nutritional neuropathy), streptococcal meningitis,
 striatonigral degeneration, stroke, strongyloidiasis, sturge-weber disease (Krabbe-Weber-
 Dimitri disease), stutter, subacute combined degeneration of the spinal cord, subacute motor
 neuronopathy, subacute necrotic myelopathy, subacute sclerosing panencephalitis, subacute
 sensory neuronopathy, subarachnoid hemorrhage, subcortical aphasia, subfalcine herniation
 25 syndrome, substance abuse, substance related disorders, sudanophilic leukoencephalopathy,
 outdystrophies, sudden infant death syndrome, suicide, sulfatide lipidosis, susto, espanto,
 meado, sydenham chorea, symmetric neuropathy associated with carcinoma, sympathotonic
 orthostatic hypotension, syncope, syndromes related to a cultural emphasis on learnt
 dissociation, syndromes related to a cultural emphasis on presenting a physical appearance
 30 pleasing to others (taijin-kyofu reactions), syndromes related to acculturative stress,

- syringobulbia, syringomyelia, systemic lupus erythematosus, tachycardia, tachypnea, Tangier disease, tardive dyskinesia, Tay-sachs disease, telangiectasia, telencephalic leukoencephalopathy, telephone scatologia, temporal lobe epilepsy, temporoparietal dementia, tension-type headache, teratomas, tetanus, tetany, thalamic syndrome, thallium poisoning, thoracic tumors, thrombotic thrombocytopenic purpura, thyroid disorders, tic disorders, tick paralysis, tick-borne encephalitis, tinnitus, toxic maculopathy, tonic seizures, tonic-clonic seizures, torticollis, Tourette syndrome, toxic neuropathies, toxoplasmosis, transcortical motor aphasia, transcortical sensory aphasia, transient epileptic amnesia, transient global amnesia, transitional sclerosis, transvestic fetishism, traumatic brain injury, traumatic neuroma, traumatic mutism, tremors, trichinosis, trichotillomania, trigeminal neuralgia, trochlear nerve palsy, tropical ataxic neuropathy, tropical spastic paraparesis, trypanosomiasis, tuberculomas, tuberculous meningitis, tuberous sclerosis, tumors, Turner's syndrome, typhus fever, ulegyria, uncinata fits, Unverricht-Lundborg's disease, upper airway resistance syndrome, upward transtentorial herniation syndrome, uremic encephalopathy, uremic neuropathy, urophilia, vaccinia, varicella-zoster, vascular dementia, vascular malformations, vasculitic neuropathies, vasogenic edema, velocardiofacial syndrome, venous malformations, ventilatory arrest, vertigo, vincristine toxicity, viral infections, visuospatial impairment, Vogt-Knock outyanagi-Harada syndrome, Von Hippel-Lindau disease, Von Racklinghausen disease, voyeurism, Waldenström's macroglobulinemia, Walker-Warburg syndrome, Wallenburg's syndrome, Walleyed syndrome, Weber's syndrome, Wernicke's encephalopathy, Werdnig-Hoffmann disease, Wernicke's encephalopathy, Wernicke-Knock outsaknock outff syndrome, Wernicke's aphasia, West's syndrome, whipple disease, Williams syndrome, Wilson disease, windigo, witiknock out, witigo, withdrawal with grand mal seizures, withdrawal with perceptual disturbances, withdrawal without complications, Wolman disease, xeroderma pigmentosum, xyy syndrome, Zellweger syndrome.

Behavioral Disorders

- In humans, as in other animals, behaviors related to survival, avoidance of injury, maintenance of bodily function, and reproduction are in large part instinctive. These

behaviors are caused by powerful drives, such as hunger, thirst, sleep, and sexual desire. Emotions, such as fear or joy, are also closely linked with the parts of our lives governed by instincts.

As behaviors begin to involve higher mental functions, they include a broader
5 mixture of features related to both "nature" and "nurture." The impact of learning, experience, and environment then becomes layered upon such instinctive behaviors as curiosity, attention and pleasure.

The intensity of a particular drive or emotion is highly variable from one person to another. There is also variation in the extent to which different individuals experience
10 particular drives and emotions. For instance, one person may experience hunger more frequently than another, or feel more anxious or stressed.

There also are differences in how one responds to drives and emotions. For example, anxiety in a stressful circumstance might motivate a person to gain control of the matter, while in another, the same feelings might cause a behavior directed at avoiding the
15 situation altogether.

Basic drives and emotions are components of everyday life, and are important to one's physical and psychological well-being. Abnormalities in any of them may profoundly affect an individual's ability to think, feel and act. Behavioral problems are also very common. More individuals are afflicted every year by these conditions than by cancer and
20 heart diseases combined.

Eating Disorders

Nearly one-quarter of the U.S. Population (60 million people) is now classified as obese. Despite the fact that Americans spend about \$40 billion per year on weight-loss
25 treatments, only a small percentage of people can lose weight and keep it off. Since obesity is a direct contributor to cardiovascular disease and diabetes, there is need to address the extreme forms of these behaviors as life-threatening conditions.

Eating disorders such as anorexia nervosa and bulimia nervosa affect over a million Americans. These disorders are characterized by a constant preoccupation with food and a
30 fear of fatness. Current treatments for anorexia nervosa include hospitalization, high caloric

diet, and psychological counseling. In the case of bulimia nervosa, psychiatric treatment and antidepressant medications are being prescribed. The success rate in both cases is low.

Sleep Disorders

5 The most common sleeping problems are insomnia and narcolepsy. Insomnia is the continued inability to fall asleep or stay asleep. Almost everyone occasionally suffers from short-term insomnia. However, for people who suffer chronically from the insomnia, the disease can severely disrupt their ability to function. Narcolepsy, on the other hand, is the sudden, irresistible daytime episodes of sleepiness. People with narcolepsy have frequent
10 “sleep attacks” at various times of the day, even if they have had a normal amount of night-time sleep.

 The main anti-insomniac drugs in use today are benzodiazepine products (sleeping pills). Benzodiazepines, although somewhat effective for short-term insomnia, are not indicated for mild or severe insomnia, as they have several side effects and can cause
15 physical dependence. For narcolepsy, there is presently no cure. Stimulants, like amphetamines, can help reduce the symptoms, but do not alleviate them entirely.

Sexual Disorders

 Tens of millions of men have some form of erectile dysfunction (impotence) —
20 mild, moderate, severe, acute, or chronic. An even larger number of women are estimated to suffer from sexual arousal (inability to attain or maintain sexual excitement) and orgasmic (lack of orgasm during sex) disorders. Several million American men and women have symptoms of compulsive sexual disorder (sex addiction).

 Sexual disorders can be caused by either physical or psychological factors. There
25 are effective medicines today (such as VIAGRA™) to treat certain disorders associated with physical factors. This is not the case, however, for individuals suffering from sexual disorders involving libido. There are no drugs available to help another 5-6 million men with impotency, who do not benefit from VIAGRA™, or millions of other with sexual arousal, orgasmic, or compulsive sexual disorders.

30

Anxiety Disorders

Personal anxieties and fears are part of everyday life. For millions of individuals, however, anxieties and fears are overwhelming and persistent, often drastically interfering with daily life. These people suffer from anxiety disorders, a widespread group of illnesses
5 that can be terrifying and crippling. These conditions include panic disorder, phobias, obsessive-compulsive disorder, post-traumatic stress disorder, and generalized anxiety disorder.

Current pharmacologic treatments for anxiety include tranquilizers or anxiolytic drug (e.g., valium, and tranxene) and antidepressants. While these medications can be
10 effective at relieving anxiety symptoms, they also carry undesirable side effects such as sedation, fatigue, weight gain, sexual difficulties, and withdrawal reactions.

Mood Disorders

Depression is the most commonly diagnosed emotional problem. Each year,
15 millions of people will suffer from a depressive illness, such as major depression, or bipolar disorder. As many as one in five Americans will have at least one episode of depression during their lifetime. Many of them will be incapacitated for weeks or months.

The treatment of depression today is not much different than it was many years ago. The current antidepressants are no more efficacious than the older ones. They are improved
20 in terms of certain side effects, but they still cause sexual dysfunction, require an extended period to become effective, and cannot be mixed with several other commonly used medications.

Memory Impairments

25 Over a million Americans suffer from memory deficits beyond that expected for their age. These people are suffering from mild cognitive impairment or from dementia.

Memory loss, particularly of recent events, is the prevailing symptom of mild cognitive impairment. Dementia is a more severe condition. People with dementia suffer from short-term memory loss, inability to think through or complete complex tasks without
30 step-by-step instructions, confusion, difficulty concentrating, and paranoid, inappropriate, or

bizarre behavior. Currently, there are no medications available to treat or prevent memory impairments.

Attention Disorders

5 As many as a million school-age children in the U.S. are claimed to suffer from attention-deficit hyperactivity disorder (ADHD). The disease has its onset in childhood and is characterized by lack of attention, impulsiveness, and hyperactivity. ADHD often continues into adolescence and adulthood. The disease has long-term adverse affects on success at school, work, and in social relationships. Stimulants are used to treat the
10 symptoms of ADHD. Children with the disorder seldom outgrow it, and long-term therapy is not advised.

Pain

 Pain arises in response to a noxious stimulus or tissue injury. In some instances,
15 pain may continue after the tissue damage has healed or in the absence of evident tissue damage. This is chronic pain. Millions of Americans have some form of persisting or recurring pain. They usually suffer from tension or migraine headaches, low back pain, or arthritis. Chronic pain is also a byproduct of heart diseases and cancer. Chronic pain is often unresponsive to conventional therapies. People with chronic pain are treated with a
20 wide variety of medications, usually with limited success.

Substance Abuse/Addiction

 Substance abuse and addiction are considered to be one of the serious social issues in modern times. Despite growing efforts to address them, there are no effective
25 medications available to treat most people with substance abuse and addiction problems. People who abuse substances, but are not yet addicted to them, are usually treated with behavioral therapies. Treatment of addicted people often involves a combination of behavior therapy and medication. In either case, the results are poor. Only a minority is helped by these treatments.

30

GPCR expression in non-neural tissues

Adrenal gland. GPCRs expressed in the adrenal gland are listed in Table 15. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of a GPCR in the adrenal gland. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the adrenal gland, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 15. GPCRs Expressed in the Adrenal Gland

| | | | | | |
|-----------|----------|---------|---------|-----------|----------|
| ADCYAP1R1 | CCXCR1 | FZD1 | GPR49 | HUMNP1Y20 | PGR4 |
| ADMR | CD97 | FZD10 | GPR54 | IL8RA | PGR7 |
| ADORA1 | CELSR1 | FZD2 | GPR55 | KIAA0758 | PGR8 |
| ADORA2A | CELSR2 | FZD3 | GPR63 | KIAA1828 | PTAFR |
| ADORA2B | CHRM1 | FZD4 | GPR64 | LEC1 | PTGER1 |
| ADORA3 | CHRM3 | FZD5 | GPR65 | LEC2 | PTGER2 |
| ADRA1A | CHRM4 | FZD6 | GPR75 | LEC3 | PTGER3 |
| ADRA1D | CMKBR1L2 | FZD8 | GPR77 | MC2R | PTGER4 |
| ADRA2B | CMKLR1 | FZD9 | GPR80 | MC5R | PTGFR |
| ADRB1 | CNR1 | G2A | GPR81 | MRG | PTGIR |
| ADRB2 | CNR2 | GABBR1 | GPR82 | MRGE | PTHR1 |
| ADRB3 | CX3CR1 | GCGR | GPR83 | MRGF | PTHR2 |
| AGR9 | CXCR4 | GIPR | GPR84 | MrgG | RAI3 |
| AGTR1 | CXCR6 | GPCR150 | GPR85 | NPY2R | RDC1 |
| AGTR2 | CYSLT1 | GPR1 | GPR86 | NTSR2 | RE2 |
| AGTRL1 | CYSLT2 | GPR10 | GPR9 | OA1 | SCTR |
| AVPR1A | DJ287G14 | GPR105 | GPR91 | OPN1MW | SMOH |
| AVPR2 | DRD2 | GPR17 | GPR92 | OPN3 | SSTR2 |
| BAI2 | DRD4 | GPR18 | GPRC5B | OXTR | SSTR4 |
| BDKRB1 | EBI2 | GPR19 | GPRC5C | P2RY1 | SSTR5 |
| BDKRB2 | EDG1 | GPR21 | GPRC5D | P2RY12 | TACR2 |
| C3AR1 | EDG2 | GPR22 | GRM4 | P2RY4 | TBXA2R |
| C5R1 | EDG3 | GPR23 | GRM5 | P2RY6 | TEM5 |
| CALCRL | EDG4 | GPR24 | GRPR | P2Y10 | TM7SF1 |
| CASR | EDG5 | GPR27 | H963 | P2Y5 | TM7SF1L1 |
| CCBP2 | EDG6 | GPR30 | HCRTR1 | PGR13 | TM7SF1L2 |
| CCKAR | EDG7 | GPR31 | HCRTR2 | PGR15 | TM7SF3 |
| CCR1 | EDNRA | GPR34 | HGPCR11 | PGR16 | TPRA40 |
| CCR2 | EDNRB | GPR35 | HM74 | PGR17 | TRHR2 |
| CCR4 | EMR1 | GPR37 | HRH1 | PGR20 | TSHR |
| CCR5 | ETL | GPR37L1 | HRH2 | PGR21 | VLGR1 |
| CCR6 | F2R | GPR39 | HRH3 | PGR22 | |
| CCR7 | F2RL2 | GPR4 | HTR1B | PGR25 | |
| CCR8 | F2RL3 | GPR43 | HTR1D | PGR26 | |

| | | | | | |
|-------|--------|-------|-------|-------|--|
| CCR9 | FKSG79 | GPR44 | HTR2A | PGR27 | |
| CCRL1 | FY | GPR48 | HTR2B | PGR28 | |

Exemplary diseases and disorders of the adrenal gland include 11-hydroxylase deficiency, 17-hydroxylase deficiency, 3 β -dehydrogenase deficiency, acquired immune

5 deficiency syndrome, ACTH-dependent adrenal hyperfunction (Cushing disease), ACTH-independent adrenal hyperfunction, acute adrenal insufficiency, adrenal abscess, adrenal adenoma, adrenal calcification, adrenal cysts, adrenal cytomegaly, adrenal dysfunction in glycerol kinase deficiency, adrenal hematoma, adrenal hemorrhage, adrenal histoplasmosis, adrenal hyperfunction, adrenal hyperplasia, adrenal medullary hyperplasia, adrenal

10 myelolipoma, adrenal tuberculosis, adrenocortical adenoma, adrenocortical adenoma with primary hyperaldosteronism (Conn's syndrome), adrenocortical carcinoma, adrenocortical carcinoma with Cushing's syndrome, adrenocortical hyperfunction, adrenocortical insufficiency, adrenocortical neoplasms, adrenoleukodystrophy, amyloidosis, anencephaly, autoimmune Addison's disease, Beckwith-Wiedemann syndrome, bilateral

15 adrenal hyperplasia, chronic insufficiency of adrenocortical hormone synthesis, complete 21-hydroxylase deficiency, congenital adrenal hyperplasia, congenital adrenal hypoplasia, cortical hyperplasia, desmolase deficiency, ectopic ACTH syndrome, excess aldosterone secretion, excess cortisol secretion (Cushing's syndrome), excess secretion of adrenocortical hormones, excess sex hormone secretion, familial glucocorticoid deficiency, functional

20 "black" adenomas, ganglioneuroblastoma, ganglioneuroma, glucocorticoid remediable hyperaldosteronism, herpetic adrenalitis, hyperaldosteronism, idiopathic Addison's disease, idiopathic hyperaldosteronism with bilateral hyperplasia of zona glomerulosa, iatrogenic hypercortisolism, lysosomal storage diseases, macronodular hyperplasia, macronodular hyperplasia with marked adrenal enlargement, malignant lymphoma, malignant melanoma,

25 metastatic carcinoma, metastatic tumors, micronodular hyperplasia, multiple endocrine neoplasia syndromes, multiple endocrine neoplasia type 1 (Wermer syndrome), multiple endocrine neoplasia type 2a (Sipple syndrome), multiple endocrine neoplasia type 2b, neuroblastoma, Niemann-Pick disease, ovarian thecal metaplasia, paraganglioma, partial 21-hydroxylase deficiency, pheochromocytoma, primary aldosteronism (Conn's syndrome),

primary chronic adrenal insufficiency (Addison's disease), primary hyperaldosteronism, primary mesenchymal tumors, primary pigmented nodular adrenocortical disease, salt-wasting congenital adrenal hyperplasia, secondary Addison's disease, secondary hyperaldosteronism, selective hypoaldosteronism, simple virilizing congenital adrenal hyperplasia, Waterhouse-Friderichsen syndrome, and Wolman's disease.

Colon. GPCRs expressed in the colon are listed in Table 16. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of these GPCRs in the colon. These polypeptides, or polymorphs of these polypeptides, may form the basis of therapeutic regimen or a diagnostic test to determine, e.g., the presence of disease or disorder involving the colon, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 16. GPCRs Expressed in the Colon

| | | | | | |
|---------|----------|----------|---------|----------|--------|
| ADORA2A | CHRM2 | F2RL1 | GPR35 | HTR1F | PTAFR |
| ADORA2B | CHRM3 | F2RL2 | GPR37L1 | HTR2B | PTGER1 |
| ADORA3 | CHRM4 | F2RL3 | GPR39 | HTR4 | PTGER2 |
| ADRA2A | CMKBR1L2 | FLJ14454 | GPR4 | KIAA0758 | PTGER3 |
| ADRA2B | CMKLR1 | FY | GPR43 | LEC1 | PTGER4 |
| AGR9 | CNR2 | FZD1 | GPR48 | LEC3 | PTHR2 |
| AGTRL1 | CX3CR1 | FZD4 | GPR49 | MRG | RAI3 |
| BDKRB2 | CXCR4 | FZD5 | GPR54 | MRGE | RDC1 |
| BLR1 | CXCR6 | FZD6 | GPR57 | MRGF | RE2 |
| C5R1 | CYSLT1 | FZD8 | GPR66 | NTSR1 | SSTR1 |
| CALCRL | CYSLT2 | G2A | GPR73 | OPN3 | SSTR3 |
| CCBP2 | DJ287G14 | GABBR1 | GPR77 | P2RY1 | SSTR4 |
| CCKAR | EBI2 | GLP1R | GPR81 | P2RY12 | SSTR5 |
| CCR1 | EDG1 | GLP2R | GPR82 | P2RY2 | TACR2 |
| CCR2 | EDG2 | GPCR150 | GPR85 | P2RY6 | TEM5 |
| CCR3 | EDG3 | GPR105 | GPR86 | P2Y10 | TM7SF1 |
| CCR5 | EDG4 | GPR18 | GPR9 | P2Y5 | TM7SF3 |
| CCR6 | EDG5 | GPR20 | GPR92 | PGR16 | TPRA40 |
| CCR7 | EDG7 | GPR21 | GPRC5B | PGR19 | TRHR2 |
| CCR9 | EDNRA | GPR22 | GPRC5C | PGR21 | VIPR1 |
| CCRL1 | EDNRB | GPR24 | GRCA | PGR22 | VIPR2 |
| CD97 | EMR1 | GPR30 | H963 | PGR25 | VLGR1 |
| CELSR1 | ETL | GPR31 | HCRTR1 | PGR27 | |
| CHRM1 | F2R | GPR34 | HRH1 | PGR4 | |

Exemplary diseases and disorders involving the colon include acute self-limited infectious colitis, adenocarcinoma, adenoma, adenoma-carcinoma sequence, adenomatous polyposis coli, adenosquamous carcinomas, allergic (eosinophilic) proctitis and colitis,

5 amebiasis, amyloidosis, angiodysplasia, anorectal malformations, blue rubber bleb nevus syndrome, brown bowel syndrome, *Campylobacter fetus* infection, carcinoid tumors, carcinoma of the anal canal, carcinoma of the colon and rectum, chlamidial proctitis, Crohn's disease, clear cell carcinomas, *Clostridium difficile* pseudomembranous enterocolitis, collagenous colitis, colonic adenoma, colonic diverticulosis, colonic inertia,

10 colonic ischemia, congenital atresia, congenital megacolon (Hirschsprung's disease), congenital stenosis, constipation, Cowden's syndrome, cystic fibrosis, cytomegalovirus colitis, diarrhea, dieulafor lesion, diversion colitis, diverticulitis, diverticulosis, drug-induced diseases, dysplasia and malignancy in inflammatory bowel disease, Ehlers-Danlos syndromes, enterobiasis, familial adenomatous polyposis, familial polyposis syndromes,

15 Gardner's syndrome, gastrointestinal stromal neoplasms, hemangiomas and vascular anomalies, hemorrhoids, hereditary hemorrhagic telangiectasia, herpes colitis, hyperplastic polyps, idiopathic inflammatory bowel disease, incontinence, inflammatory bowel syndrome, inflammatory polyps, inherited adenomatous polyposis syndromes, intestinal hamartomas, intestinal pseudo-obstruction, irritable bowel syndrome, ischemic colitis,

20 juvenile polyposis, juvenile polyps, Klippel-Trénaunay-Weber syndrome, leiomyomas, lipomas, lymphocytic (microscopic) colitis, lymphoid hyperplasia and lymphoma, malaknock outplakia, malignant lymphoma, malignant neoplasms, malrotation, metastatic neoplasms, mixed hyperplastic and adenomatous polyps, mucosal prolapse syndrome, neonatal necrotizing enterocolitis, neuroendocrine cell tumors, neurogenic tumors,

25 neutropenic enterocolitis, non-neoplastic polyps, Peutz-Jeghers syndrome, pneumatosis cystoides intestinalis, polyposis coli, pseudomembranous colitis, pseudoxanthoma elasticum, pure squamous carcinomas, radiation colitis, schistosomiasis, *Shigella* colitis (bacillary dysentery), spindle cell carcinomas, spirochetosis, stercoral ulcers, stromal tumors, systemic sclerosis and CREST syndrome, trichuriasis, tubular adenoma

30 (adenomatous polyp, polypoid adenoma), Turcot's syndrome, Turner's syndrome,

ulcerative colitis, villous adenoma, and volvulus.

Heart. GPCRs expressed in the heart are listed in Table 17. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of any of these GPCRs in the heart. These polypeptides, or polymorphs of these polypeptides, may also form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of disease, the risk of developing a particular cardiovascular disease or disorder, or an appropriate therapeutic course.

10

Table 17. GPCRs Expressed in the Heart

| | | | | | |
|-----------|----------|---------|---------|----------|----------|
| ADCYAP1R1 | CCR6 | EMR1 | GPR23 | HM74 | PGR21 |
| ADMR | CCR7 | ETL | GPR27 | HRH1 | PGR22 |
| ADORA1 | CCR8 | F2R | GPR30 | HRH2 | PGR27 |
| ADORA2A | CCRL1 | F2RL1 | GPR31 | HRH4 | PTAFR |
| ADORA2B | CCXCR1 | F2RL2 | GPR33 | HTR2B | PTGER1 |
| ADORA3 | CD97 | FKSG79 | GPR34 | KIAA0758 | PTGER2 |
| ADRA1A | CHRM2 | FPR1 | GPR35 | LEC1 | PTGER3 |
| ADRA1D | CHRM3 | FPR-RS2 | GPR4 | LGR6 | PTGER4 |
| ADRA2B | CHRM4 | FY | GPR43 | LGR7 | PTGFR |
| ADRB1 | CMKLR1 | FZD1 | GPR48 | LHCGR | PTGIR |
| ADRB2 | CNR1 | FZD2 | GPR49 | LTB4R | PTHR2 |
| AGTR1 | CNR2 | FZD3 | GPR54 | MAS1 | RAI3 |
| AGTR2 | CRHR2 | FZD4 | GPR63 | MC2R | RDC1 |
| AGTRL1 | CX3CR1 | FZD5 | GPR65 | MRGE | RRH |
| AVPR1A | CXCR4 | FZD6 | GPR73L1 | MRGF | SMOH |
| AVPR2 | CXCR6 | G2A | GPR75 | MrgG | SREB3 |
| BAI2 | CYSLT1 | GABBR1 | GPR77 | NTSR2 | SSTR2 |
| BDKRB2 | DJ287G14 | GLP1R | GPR81 | OPN1MW | SSTR4 |
| BLR1 | DRD2 | GPCR150 | GPR82 | OPN3 | TEM5 |
| C3AR1 | EBI2 | GPR1 | GPR83 | OPN4 | TM7SF1 |
| C5R1 | EDG1 | GPR105 | GPR86 | P2RY1 | TM7SF1L1 |
| CALCRL | EDG2 | GPR12 | GPR90 | P2RY12 | TM7SF1L2 |
| CASR | EDG3 | GPR14 | GPRC5B | P2RY2 | TM7SF3 |
| CCKAR | EDG5 | GPR15 | GPRC5C | P2RY6 | TPRA40 |
| CCR1 | EDG6 | GPR18 | GPRC6A | P2Y5 | TRHR2 |
| CCR2 | EDG7 | GPR2 | GRCA | PGR1 | TSHR |
| CCR4 | EDNRA | GPR21 | GRPR | PGR11 | |
| CCR5 | EDNRB | GPR22 | H963 | PGR20 | |

Cardiovascular diseases and disorders include, for example, acute coronary

syndrome, acute idiopathic pericarditis, acute rheumatic fever, American trypanosomiasis (Chagas' disease), angina pectoris, ankylosing spondylitis, anomalous pulmonary venous connection, anomalous pulmonary venous drainage, aortic atresia, aortic regurgitation, aortic stenosis, aortic valve insufficiency, aortopulmonary septal defect, asymmetric septal
 5 hypertrophy, asystole, atrial fibrillation, atrial flutter, atrial septal defect, atrioventricular septal defect, autoimmune myocarditis, bacterial endocarditis, calcific aortic stenosis, calcification of the aortic valve, calcification of the valve ring, carcinoid heart disease, cardiac amyloidosis, cardiac arrhythmia, cardiac failure, cardiac myxoma, cardiac rejection, cardiac tamponade, cardiogenic shock, cardiomyopathy of pregnancy, chronic adhesive
 10 pericarditis, chronic constrictive pericarditis, chronic left ventricular failure, coarctation of the aorta, complete heart block, complete transposition of the great vessels, congenital bicuspid aortic valves, congenital narrowing of the left ventricular outflow tract, congenital pulmonary valve stenosis, congenitally corrected transposition of the great arteries, congestive heart failure, constrictive pericarditis, cor pulmonale, coronary artery origin from
 15 pulmonary artery, coronary atherosclerosis, dilated (congestive) cardiomyopathy, diphtheria, double inlet left ventricle, double outlet right ventricle, Ebstein's malformation, endocardial fibroelastosis, endocarditis, endomyocardial fibrosis, eosinophilic endomyocardial disease (Löffler endocarditis), fibroma, glycogen storage diseases, hemochromatosis, hypertensive heart disease, hyperthyroid heart disease, hypertrophic
 20 cardiomyopathy, hypothyroid heart disease, idiopathic dilated cardiomyopathy, idiopathic myocarditis, infectious myocarditis, infective endocarditis, ischemic heart disease, left ventricular failure, Libman-Sachs endocarditis, lupus erythematosus, Lyme disease, marantic endocarditis, metastatic tumors, mitral insufficiency, mitral regurgitation, mitral stenosis, mitral valve prolapse, mucopolysaccharidoses, multifocal atrial tachycardia, myocardial
 25 infarction, myocardial ischemia, myocardial rupture, myocarditis, myxomatous degeneration, nonatheromatous coronary artery disease, nonbacterial thrombotic endocarditis, noninfectious acute pericarditis, nonviral infectious pericarditis, obliterative cardiomyopathy, patent ductus arteriosus, pericardial effusion, pericardial tumors, pericarditis, persistent truncus arteriosus, premature ventricular contraction, progressive
 30 infarction, pulmonary atresia with intact ventricular septum, pulmonary atresia with

ventricular septal defect, pulmonary insufficiency, pulmonary regurgitation, pulmonary
 stenosis, pulmonary valve lesions, pulmonary valve stenosis, pyogenic pericarditis, Q fever,
 radiations myocarditis, restrictive cardiomyopathy, rhabdomyoma, rheumatic aortic
 stenosis, rheumatic heart disease, rocky mountain spotted fever, rupture of the aortic valve,
 5 sarcoid myocarditis, scleroderma, shingolipidoses, sinus brachycardia, sudden death,
 syphilis, systemic embolism from mural thrombi, systemic lupus erythematosus, tetralogy
 of fallot, thiamine deficiency (Beriberi) heart disease, thoracic outlet syndrome, Torsade de
 Pointes, toxic cardiomyopathy, toxic myocarditis, toxoplasmosis, trichinosis, tricuspid
 atresia, tricuspid insufficiency, tricuspid regurgitation, tricuspid stenosis, tricuspid valve
 10 lesions, tuberculos pericarditis, typhus, ventricular aneurysm, ventricular fibrillation,
 ventricular septal defect, ventricular tachycardia, ventriculoarterial septal defect, viral
 pericarditis, and Wolff-Parkinson-White syndrome.

Intestine. GPCRs expressed in the intestine are listed in Table 18. These receptors
 15 are thus potential targets for therapeutic compounds that may modulate the activity,
 expression, or stability of the GPCR in the intestine. These polypeptides, or polymorphs of
 these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to
 determine, e.g., the presence of disease or disorder involving the intestine, the risk of
 developing a particular disease or disorder involving the intestine, or an appropriate
 20 therapeutic course.

Table 18. GPCRs Expressed in the Intestine

| | | | | | |
|---------|----------|----------|---------|----------|--------|
| ADORA1 | CELSR3 | FLJ14454 | GPR34 | HRH1 | PGR21 |
| ADORA2A | CHRM1 | FPR-RS2 | GPR35 | HRH2 | PGR22 |
| ADORA2B | CHRM2 | FY | GPR37L1 | HTR2B | PGR25 |
| ADORA3 | CHRM3 | FZD1 | GPR39 | IL8RA | PGR26 |
| ADRA2A | CHRM4 | FZD2 | GPR4 | KIAA0758 | PGR27 |
| ADRA2B | CMKBR1L2 | FZD3 | GPR43 | LEC1 | PGR7 |
| ADRB1 | CMKLR1 | FZD4 | GPR48 | LEC2 | PTAFR |
| ADRB2 | CX3CR1 | FZD5 | GPR49 | LEC3 | PTGER1 |
| AGTRL1 | CXCR4 | FZD6 | GPR54 | LTB4R | PTGER2 |
| AVPR2 | CXCR6 | FZD8 | GPR55 | LTB4R2 | PTGER3 |
| BDKRB2 | CYSLT1 | G2A | GPR56 | MRG | PTGER4 |

| | | | | | |
|--------|----------|---------|--------|--------|----------|
| BLR1 | CYSLT2 | GABBR1 | GPR57 | MRGE | PTGIR |
| C3AR1 | DJ287G14 | GALR1 | GPR65 | MRGF | PTHR2 |
| C5R1 | EBI2 | GALR3 | GPR66 | MTNR1A | RAI3 |
| CALCRL | EDG1 | GIPR | GPR73 | NMU2R | RDC1 |
| CCBP2 | EDG2 | GLP1R | GPR77 | NTSR1 | RE2 |
| CCKAR | EDG3 | GPCR150 | GPR81 | OPRM1 | SMOH |
| CCR1 | EDG4 | GPR105 | GPR82 | P2RY1 | SSTR2 |
| CCR3 | EDG5 | GPR18 | GPR86 | P2RY12 | TACR1 |
| CCR5 | EDG7 | GPR19 | GPR9 | P2RY2 | TEM5 |
| CCR6 | EDNRB | GPR2 | GPR92 | P2RY6 | TM7SF1 |
| CCR7 | EMR1 | GPR20 | GPRC5B | P2Y10 | TM7SF1L1 |
| CCR9 | ETL | GPR22 | GPRC5C | P2Y5 | TM7SF3 |
| CCRL1 | F2R | GPR24 | GRM4 | PGR1 | TPRA40 |
| CCXCR1 | F2RL2 | GPR27 | GRPR | PGR13 | TRHR2 |
| CD97 | F2RL3 | GPR30 | H963 | PGR15 | VIPR1 |
| CELSR1 | FKSG79 | GPR31 | HCRT1 | PGR16 | VIPR2 |

- Diseases and disorders involving the intestine include abdominal hernia, abetalipoproteinemia, abnormal rotation, acute hypotensive hypoperfusion, acute intestinal ischemia, acute small intestinal infarction, adenocarcinoma, adenoma, adhesions, amebiasis, anemia, arterial occlusion, atypical mycobacteriosis, bacterial diarrhea, bacterial overgrowth type syndromes, botulism, *Campylobacter fetus* infection, *Campylobacter jejuni* infection, carbohydrate absorption defects, carcinoid tumors, celiac disease (nontropical sprue, gluten-induced enteropathy), cholera, Crohn's disease, chronic intestinal ischemia, *Clostridium difficile* pseudomembranous enterocolitis, *Clostridium perfringens* infection, congenital umbilical hernia, Cronkhite-Canada syndrome, cytomegalovirus enterocolitis, diarrhea, diarrhea caused by invasive bacteria, diverticulitis, diverticulosis, dysentery, enteroinvasive and enterohemorrhagic *Escherichia coli* infection, eosinophilic gastroenteritis, failure of peristalsis, familial polyposis syndromes, food poisoning, fungal enteritis, gangliocytic paragangliomas, Gardner's syndrome, gastrointestinal stromal neoplasms, giardiasis, hemorrhoids, hernia, hyperplastic polyps, idiopathic inflammatory bowel disease, ileus, imperforate anus, intestinal (abdominal ischemia), intestinal atresia, intestinal cryptosporidiosis, microsporidiosis & isosporiasis in AIDS, intestinal hamartomas, intestinal helminthiasis, intestinal hemorrhage, intestinal infiltrative disorders, intestinal lymphangiectasia, intestinal obstruction, intestinal perforation, intestinal reduplication, intestinal stenosis, intestinal tuberculosis,

intussusception, jejunal diverticulosis, juvenile polyposis, juvenile retention polyps, lactase deficiency, lymphomas, malabsorption syndrome, malignant lymphoma, malignant neoplasms, malrotations, mechanical obstruction, Meckel's diverticulum, meconium ileus, mediterranean lymphoma, mesenchymal tumors, mesenteric vasculitis, mesenteric vein

5 thrombosis, metastatic neoplasms, microvillus inclusion disease, mixed hyperplastic and adenomatous polyps, neonatal necrotizing enterocolitis, nodular duodenum, nonocclusive intestinal ischemia, nonspecific duodenitis, nontyphoidal salmonellosis, omphalocele, parasitic infections, peptic ulcer disease, Peutz-Jeghers syndrome, pneumatosis cystoides intestinalis, poorly differentiated neuroendocrine carcinomas, primary lymphoma, protein-

10 losing enteropathy, Salmonella gastroenteritis, sarcoidosis, sarcomas, shigellosis, staphylococcal food poisoning, steatorrhea, sugar intolerance, thrombosis of the mesenteric veins, toxigenic diarrhea, toxigenic *Escherichia coli* infection, tropical sprue, tubular adenoma (adenomatous polyp, polypoid adenoma), typhoid fever, ulcers, vascular malformations, villous adenoma, viral enteritis, viral gastroenteritis, visceral myopathy,

15 visceral neuropathy, vitelline duct remnants, volvulus, Western-type intestinal lymphoma, Whipple's disease (intestinal lipopystrophy), *Yersinia enterocolitica* & *Yersinia pseudotuberculosis* infection, and Zollinger-Ellison syndrome.

Kidney. GPCRs expressed in the kidney are listed in Table 19. These receptors are

20 thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the kidney. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of disease, the risk of developing a particular kidney disease or disorder, or an appropriate therapeutic course.

25

Table 19. GPCRs Expressed in the Kidney

| | | | | | |
|-----------|--------|-------|-------|----------|--------|
| ADCYAP1R1 | CCR7 | F2R | GPR24 | KIAA0758 | PGR8 |
| ADMR | CD97 | F2RL1 | GPR30 | LEC1 | PTAFR |
| ADORA1 | CELSR1 | F2RL2 | GPR31 | LTB4R | PTGDR |
| ADORA2A | CELSR2 | F2RL3 | GPR34 | LTB4R2 | PTGER1 |

| | | | | | |
|---------|----------|---------|------------|-------|----------|
| ADORA2B | CHRM1 | FKSG79 | GPR35 | MAS1 | PTGER3 |
| ADRA1A | CHRM3 | FPR-RS2 | GPR39 | MC2R | PTGER4 |
| ADRA1B | CMKLR1 | FZD1 | GPR4 | MC4R | PTGFR |
| ADRA1D | CNR1 | FZD2 | GPR41 | MRG | PTGIR |
| ADRA2B | CNR2 | FZD4 | GPR48 | MRGE | PTHR1 |
| ADRB1 | CX3CR1 | FZD5 | GPR49 | MRGF | RAI3 |
| ADRB2 | CXCR4 | FZD6 | GPR54 | NPY6R | RDC1 |
| AGTR1 | CXCR6 | FZD7 | GPR63 | OPN3 | SMOH |
| AGTR2 | CYSLT1 | FZD8 | GPR65 | OPRL1 | SREB3 |
| AGTRL1 | DJ287G14 | G2A | GPR80 | P2RY1 | TBXA2R |
| AVPR2 | EBI2 | GABBR1 | GPR81 | P2RY2 | TEM5 |
| BDKRB1 | EDG1 | GALR3 | GPR84 | P2RY6 | TM7SF1 |
| BLR1 | EDG2 | GCCR | GPR85 | P2Y10 | TM7SF1L1 |
| C3AR1 | EDG3 | GHRHR | GPR91 | P2Y5 | TM7SF3 |
| CALCR | EDG4 | GLP1R | GPR92 | PGR1 | TPRA40 |
| CALCRL | EDG5 | GPCR150 | GPRC5B | PGR16 | TRHR2 |
| CASR | EDG6 | GPR105 | GPRC5C | PGR19 | TSHR |
| CCKAR | EDG7 | GPR18 | GRCA | PGR20 | VIPR2 |
| CCR1 | EDNRA | GPR19 | HM74 | PGR21 | |
| CCR2 | EDNRB | GPR2 | HTR1B | PGR22 | |
| CCR5 | EMR1 | GPR21 | HTR2B | PGR25 | |
| CCR6 | ETL | GPR23 | HUMNPIIY20 | PGR7 | |

- Exemplary diseases and disorders of the kidney include acquired cystic disease, acute (postinfectious) glomerulonephritis, acute infectious interstitial nephritis, acute
- 5 interstitial nephritis, acute pyelonephritis, acute renal failure, acute transplant failure, acute tubular necrosis, adult polycystic kidney disease, AL amyloid, analgesic nephropathy, anti-glomerular basement membrane disease (Goodpasture's Syndrome), asymptomatic hematuria, asymptomatic proteinuria, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, Bence Jones cast nephropathy, benign
- 10 familial hematuria, benign nephrosclerosis and atheromatous embolization, bilateral cortical necrosis, chronic glomerulonephritis, chronic interstitial nephritis, chronic pyelonephritis, chronic renal failure, chronic transplant failure, circulating immune complex nephritis, crescentic glomerulonephritis, cryoglobulinemia, cystic renal dysplasia, diabetic glomerulosclerosis, diabetic nephropathy, dialysis cystic disease, drug induced (allergic)
- 15 acute interstitial nephritis, ectopic kidney, Fabry's disease, familial juvenile nephronophthisis-medullary cystic disease complex, focal glomerulosclerosis (segmental hyalinosis), glomerulocystic disease, glomerulonephritis, glomerulonephritis associated

with bacterial endocarditis, glomerulosclerosis, hemolytic-uremic syndrome, Henoch-Schönlein purpura, hepatitis-associated glomerulonephritis, hereditary nephritis (Alport syndrome), horseshoe kidney, hydronephrosis, IgA nephropathy, infantile polycystic kidney disease, ischemic acute tubular necrosis, light-chain deposit disease, malignant

5 nephrosclerosis, medullary cystic disease, membranoproliferative (mesangiocapillary) glomerulonephritis, membranous glomerulonephritis, membranous nephropathy, mesangial proliferative glomerulonephritis (includes Berger's Disease), minimal change glomerular disease, minimal change nephrotic syndrome, nephritic syndrome, nephroblastoma (Wilms tumor), nephronophthisis (medullary cystic disease complex), nephrotic syndrome, plasma

10 cell dyscrasias (monoclonal immunoglobulin-induced renal damage), polyarteritis nodosa, proteinuria, pyelonephritis, rapidly progressive (crescentic) glomerulonephritis, renal agenesis, renal amyloidosis, renal cell carcinoma, renal dysgenesis, renal dysplasia, renal hypoplasia, renal infection, renal osteodystrophy, renal stones (urolithiasis), renal tubular acidosis, renal vasculitis, renovascular hypertension, scleroderma (progressive systemic

15 sclerosis), secondary acquired glomerulonephritis, simple renal cysts, systemic lupus erythematosus, thin basement membrane nephropathy, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, toxic acute tubular necrosis, tubular defects, tubulointerstitial disease in multiple myeloma, urate nephropathy, urinary obstruction, and vasculitis.

20

Liver. GPCRs expressed in the liver are listed in Table 20. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the liver. These polypeptides, or polymorphs of these

polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine,

25 e.g., the presence of disease, the risk of developing a particular liver disease or disorder, or an appropriate therapeutic course.

Table 20. GPCRs Expressed in the Liver

| | | | | | |
|------|-------|------|-------|--------|------|
| ADMR | CCRL1 | EMR1 | GPR48 | LTB4R2 | PGR8 |
|------|-------|------|-------|--------|------|

| | | | | | |
|---------|----------|----------|----------|--------|----------|
| ADORA1 | CD97 | ETL | GPR51 | MRG | PTAFR |
| ADORA2A | CELSR1 | F2R | GPR54 | MRGE | PTGDR |
| ADRA1A | CHRM1 | F2RL2 | GPR56 | MTNR1A | PTGER2 |
| ADRA1B | CMKBR1L2 | FLJ14454 | GPR57 | OPN3 | SMOH |
| ADRA2B | CMKLR1 | FPR1 | GPR66 | OPRM1 | SSTR4 |
| ADRB1 | CNR1 | FY | GPR73 | P2RY1 | TEM5 |
| ADRB2 | CNR2 | FZD4 | GPR86 | P2RY12 | TM7SF1 |
| AGTR1 | CXCR4 | FZD6 | GPR9 | P2RY2 | TM7SF1L1 |
| AVPR1A | CYSLT1 | FZD7 | GPR91 | P2RY4 | TM7SF3 |
| AVPR2 | DJ287G14 | FZD8 | GPRC5C | P2RY6 | TPRA40 |
| BLR1 | EBI2 | G2A | GRCA | P2Y5 | VIPR1 |
| C5R1 | EDG1 | GABBR1 | H963 | PGR16 | VLGR1 |
| CALCRL | EDG2 | GCGR | HTR1D | PGR18 | |
| CCBP2 | EDG3 | GLP1R | HTR1F | PGR21 | |
| CCKAR | EDG5 | GPR19 | HTR7 | PGR22 | |
| CCR2 | EDNRA | GPR21 | IL8RA | PGR26 | |
| CCR5 | EDNRB | GPR39 | KIAA0758 | PGR7 | |

- Exemplary liver diseases and disorders include acute alcoholic hepatitis (acute sclerosing hyaline necrosis of the liver), acute graft-versus-host disease, acute hepatitis, acute hepatocellular injury associated with infectious diseases other than viral hepatitis., acute liver failure, acute viral hepatitis, adenovirus hepatitis, Alagille syndrome, alcoholic cirrhosis, alcoholic hepatitis, alcoholic liver disease, alpha 1-antitrypsin deficiency, amebic abscess, angiolmyolipoma, angiosarcoma, ascending cholangitis, autoimmune chronic active hepatitis (lupoid hepatitis), bile duct adenoma, bile duct cystadenocarcinoma, bile duct cystadenoma, biliary atresia, biliary cirrhosis, biliary papillomatosis, bridging necrosis, Budd-Chiari syndrome, Byler disease, cardiac fibrosis of the liver, Caroli disease, cavernous hemangioma, cholangiocarcinoma, cholangitic abcess, choleostasis, cholestatic viral hepatitis, chronic active hepatitis, chronic alcoholic liver disease, chronic graft-versus-host disease, chronic hepatic venous congestion, chronic hepatitis, chronic liver failure, chronic passive congestion, chronic viral hepatitis, cirrhosis, combined hepatocellular and cholangiocarcinoma, confluent hepatic necrosis, congenital hepatic fibrosis, Crigler-Najjar syndrome, cryptogenic cirrhosis, cystic fibrosis, defects of coagulation, delta hepatitis, Dubin-Johnson syndrome, epithelioid hemangioendothelioma, erythrohepatic protoporphyria, extrahepatic biliary obstruction (primary biliary cirrhosis), fatty change, fatty liver, focal necrosis, focal nodular hyperplasia, fulminant viral hepatitis, galactosemia,

Gilbert's syndrome, glycogen storage diseases, graft-versus-host disease, granulomatous hepatitis, hemangioma, hemangiosarcoma, hemochromatosis, hepatic adenoma, hepatic amebiasis, hepatic encephalopathy, hepatic failure, hepatic schistosomiasis, hepatic veno-occlusive disease, hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E,

5 hepatoblastoma, hepatocellular adenoma, hepatocellular carcinoma, hepatocellular necrosis, hepatorenal syndrome, hereditary fructose intolerance, hereditary hemochromatosis, herpesvirus hepatitis, hydatid cyst, hyperplastic lesions, hypoalbuminemia, infantile hemangioendothelioma, infarction of the liver, infectious mononucleosis hepatitis, inflammatory pseudotumor of the liver, intrahepatic cholangiocarcinoma, intrahepatic

10 cholestasis, intrahepatic portal hypertension, ischemic necrosis (ischemic hepatitis), isoniazid-induced necrosis, jaundice, leptospirosis, liver cell adenoma, liver manifestations of Rocky Mountain spotted fever, macronodular cirrhosis, macrovesicular steatosis, malignant vascular neoplasms, mass lesions, massive hepatocellular necrosis, massive necrosis, mesenchymal hamartoma, metastatic tumors, micronodular cirrhosis,

15 microvesicular steatosis, neonatal (physiologic) jaundice, neonatal hepatitis, neoplastic lesions, nodular transformation (nodular regenerative hyperplasia, nonsuppurative infections, nutritional cirrhosis, nutritional liver disease, oriental cholangiohepatitis, parasitic infestation of the liver, peliosis hepatis, porphyria cutanea tarda, portal hypertension, portal vein thrombosis, posthepatic portal hypertension, predictable (dose-

20 related) toxicity, prehepatic portal hypertension, primary biliary cirrhosis, primary sclerosing cholangitis, pyogenic liver abscess, Q-fever hepatitis, Rotor's syndrome, sclerosing bile duct adenoma, sclerosing cholangitis, secondary hemochromatosis, submassive necrosis, syphilis, toxic liver injury, tyrosinemia, undifferentiated sarcoma, unpredictable (idiosyncratic) toxicity, vascular lesions, virus-induced cirrhosis, Wilson's

25 disease, and zonal necrosis.

Lung. GPCRs expressed in the lung are listed in Table 21. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the lung. These polypeptides, or polymorphs of these polypeptides,

30 may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the

presence of a lung disease or disorder, the risk of developing such a disease or disorder, or an appropriate therapeutic course.

Table 21. GPCRs Expressed in the Lung

5

| | | | | | |
|-----------|----------|---------|---------|-----------|----------|
| ADCYAP1R1 | CD97 | FPR1 | GPR48 | HTR6 | PGR23 |
| ADMR | CELSR1 | FY | GPR54 | HTR7 | PGR25 |
| ADORA1 | CELSR2 | FZD1 | GPR55 | HUMNP1Y20 | PGR26 |
| ADORA2A | CELSR3 | FZD10 | GPR57 | IL8RA | PGR27 |
| ADORA2B | CHRM1 | FZD2 | GPR63 | IL8RB | PGR4 |
| ADORA3 | CHRM2 | FZD3 | GPR65 | KIAA0758 | PGR5 |
| ADRA1A | CHRM3 | FZD4 | GPR66 | LEC1 | PGR7 |
| ADRA1D | CMKBR1L2 | FZD5 | GPR68 | LEC2 | PGR8 |
| ADRA2A | CMKLR1 | FZD6 | GPR7 | LEC3 | PTAFR |
| ADRA2B | CNR1 | FZD7 | GPR73 | LGR6 | PTGER1 |
| ADRB1 | CNR2 | G2A | GPR75 | LGR7 | PTGER2 |
| ADRB2 | CRHR2 | GABBR1 | GPR77 | LTB4R | PTGER3 |
| ADRB3 | CX3CR1 | GALR3 | GPR80 | LTB4R2 | PTGER4 |
| AGTR1 | CXCR4 | GLP1R | GPR81 | MAS1 | PTGFR |
| AGTRL1 | CXCR6 | GPCR150 | GPR82 | MC5R | PTGIR |
| AVPR2 | CYSLT1 | GPR1 | GPR83 | MRG | PTHR1 |
| BAI2 | CYSLT2 | GPR105 | GPR84 | MRGE | RAI3 |
| BDKRB1 | DJ287G14 | GPR15 | GPR86 | MRGF | RDC1 |
| BDKRB2 | DRD2 | GPR17 | GPR9 | MrgG | RE2 |
| BLR1 | EBI2 | GPR18 | GPR92 | NPY1R | SMOH |
| C3AR1 | EDG1 | GPR19 | GPRC5B | OPN1MW | SREB3 |
| C5R1 | EDG2 | GPR2 | GPRC5C | OPN3 | SSTR1 |
| CALCR | EDG3 | GPR21 | GPRC6A | OPRD1 | SSTR2 |
| CALCRL | EDG4 | GPR23 | GRM4 | P2RY1 | SSTR4 |
| CCBP2 | EDG5 | GPR24 | GRM6 | P2RY12 | TACR1 |
| CKAR | EDG6 | GPR27 | H963 | P2RY2 | TBXA2R |
| CCR1 | EDG7 | GPR30 | HCRTR1 | P2RY4 | TEM5 |
| CCR2 | EDG8 | GPR31 | HGPCR11 | P2RY6 | TM7SF1 |
| CCR3 | EDNRA | GPR33 | HGPCR19 | P2Y10 | TM7SF1L1 |
| CCR4 | EDNRB | GPR34 | HM74 | P2Y5 | TM7SF1L2 |
| CCR5 | EMR1 | GPR35 | HRH2 | PGR1 | TM7SF3 |
| CCR6 | ETL | GPR37 | HRH4 | PGR13 | TPRA40 |
| CCR7 | F2R | GPR39 | HTR1B | PGR15 | TRHR2 |
| CCR8 | F2RL1 | GPR4 | HTR1F | PGR16 | TSHR |
| CCR9 | F2RL2 | GPR40 | HTR2A | PGR20 | VIPR2 |
| CCRL1 | F2RL3 | GPR43 | HTR2B | PGR21 | |
| CCXCR1 | FKSG79 | GPR44 | HTR4 | PGR22 | |

Exemplary lung diseases and disorders (including those of the trachea) include abnormal diffusion, abnormal perfusion, abnormal ventilation, accelerated silicosis,

actinomycosis, acute air space pneumonia (acute bacterial pneumonia), acute bronchiolitis, acute congestion, acute infections of the lung, acute interstitial pneumonia, acute necrotizing viral pneumonia, acute organic dust toxic syndrome, acute pneumonia, acute radiation pneumonitis, acute rheumatic fever, acute silicosis, acute tracheobronchitis,

5 adenocarcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, adenovirus, adult respiratory distress syndrome (shock lung), agenesis, AIDS, air embolism, allergic bronchopulmonary mycosis, allergic granulomatosis and angiitis (Churg-Strauss), allograft rejection, aluminum pneumoconiosis, alveolar microlithiasis, alveolar proteinosis, amebic lung abscess, amniotic fluid embolism, amyloidosis of the lung, anomalies of pulmonary

10 vasculature, anomalous pulmonary venous return, apiration pneumonia, aplasia, asbestosis, asbestos-related diseases, aspergillosis, asthma, atelectasis, atriovenous fistulas, atypical mycobacterial infection, bacteremia, bacterial pneumonia, benign clear cell tumor, benign epithelial tumors, benign fibrous mesothelioma, berylliosis, blastomycosis, bronchial atresia, bronchial asthma, bronchial carcinoid tumor, bronchial isomerism, bronchial

15 obstruction, bronchial stenosis, bronchiectasis, bronchiolalveolar carcinoma, bronchiolitis, bronchiolitis obliterans-organizing pneumonia, bronchocentric granulomatosis, bronchogenic cyst, bronchopneumonia, bronchopulmonary dysplasia, bronchopulmonary sequestration, bullae, bullous emphysema, cancer, carcinoid tumors, carcinoma of the lung (bronchogenic carcinoma), central (bronchogenic) carcinoma, central cyanosis, centriacinar

20 emphysema, cetrilobular emphysema, chest pain, Chlamydial pneumonia, chondroid hamartoma, chronic airflow obstruction, chronic bronchitis, chronic diffuse interstitial lung disease, chronic idiopathic pulmonary fibrosis, chronic lung abscess, chronic obstructive pulmonary diseases, chronic radiation pneumonitis, chronic silicosis, chylothorax, ciliary dyskinesia, coal worker's pneumoconiosis (anthracosis), coccidioidomycosis, collagen-

25 vascular diseases, common cold, compensatory emphysema, congenital acinar dysplasia, congenital alveolar capillary dysplasia, congenital bronchobiliary fistula, congenital bronchoesophageal fistula, congenital cystic adenomatoid malformation, congenital pulmonary lymphangiectasis, congenital pulmonary overinflation (congenital emphysema), congestion, cough, cryptococcosis, cyanosis, cystic fibrosis, cysticercosis, cytomegalovirus,

30 desquamative interstitial pneumonitis, destructive lung disease, diatomaceous earth

pneumoconiosis, diffuse alveolar damage, diffuse pulmonary hemorrhage, diffuse septal amyloidosis, diffuse panbronchiolitis, *Dirofilaria immitis*, diseases of the pleura, distal acinar (paraceptal) emphysema, drug-induced asthma, drug-induced diffuse alveolar damage, dyspnea, ectopic hormone syndromes, emphysema, empyema, eosinophilic pneumonias, exercise-induced asthma, extralobar sequestration, extrinsic allergic asthma, fat emboli, focal dust emphysema, follicular bronchiolitis, follicular bronchitis, foreign-body embolism, Fuller's earth pneumoconiosis, functional resistance to arterial flow (vasoconstriction), fungal granulomas of the lung, fungal infections, Goodpasture's syndrome, graphite pneumoconiosis, gray hepatization, hamartomas, hard metal disease, hemoptysis, hemothorax, herniation of lung tissue, herpes simplex, heterotopic tissues, high-altitude pulmonary edema, histoplasmosis, horseshoe lung, humidifier fever, hyaline membrane disease, hydatid cysts, hydrothorax, hypersensitivity pneumonitis (extrinsic allergic alveolitis), hypoxic vascular remodeling, iatrogenic drug-, chemical-, or radiation-induced interstitial fibrosis, idiopathic interstitial pneumonia, idiopathic organizing pneumonia, idiopathic pulmonary fibrosis (fibrosing alveolitis, Hamman-Rich syndrome, acute interstitial pneumonia), idiopathic pulmonary hemosiderosis, immunologic interstitial fibrosis, immunologic interstitial pneumonitis, immunologic lung disease, infections causing chronic granulomatous inflammation, infections causing chronic suppurative inflammation, infections of the air passages, infiltrative lung disease, inflammatory lesions, inflammatory pseudotumors, influenza, interstitial diseases of uncertain etiology, interstitial lung disease, interstitial pneumonitis in connective tissue diseases, intralobar sequestration of the lung (congenital), intrinsic (nonallergic) asthma, invasive pulmonary aspergillosis, kaolin pneumoconiosis, Kartagener's syndrome, *Klebsiella pneumoniae*, Langerhans' cell histiocytosis (histiocytosis X), large cell undifferentiated carcinoma, larval migration of *Ascaris lumbricoides*, larval migration of *Strongyloides stercoralis*, left pulmonary artery "sling", *Legionella pneumoniae*, lipid pneumonia, lobar pneumonia, localized emphysema, long-standing bronchial obstruction, lung abscess, lung collapse, lung fluke, lung transplantation implantation response, lymphangiomyomatosis, lymphocytic interstitial pneumonitis (pseudolymphoma, lymphoma, lymphomatoid granulomatosis, malignant mesothelioma, massive pulmonary hemorrhage in the newborn, measles, meconium

- aspiration syndrome, mesenchymal cystic hamartomas, mesenchymal tumors, mesothelioma, metal-induced lung diseases, metastatic calcification, metastatic neoplasms, metastatic ossification, mica pneumoconiosis, mixed dust fibrosis, mixed epithelial-mesenchymal tumors, mixed type neoplasms, mucoepidermoid tumor, mucoviscidosis
- 5 (fibrocystic disease of the pancreas, mycoplasma pneumoniae, necrotizing bacterial pneumonia, necrotizing sarcoid granulomatosis, neonatal respiratory distress syndrome, neoplasms of the pleura, neuromuscular syndromes, nocardiosis, nondestructive lung disease, North American blastomycosis, occupational asthma, organic dust disease, panacinar emphysema, Pancoast's syndrome, paracoccidioidomycosis, parainfluenza,
- 10 paraneoplastic syndromes, paraseptal emphysema (paracicatricial), parasilicosis syndromes, parasitic infections of the lung, peripheral cyanosis, peripheral lung carcinoma, persistent pulmonary hypertension of the newborn, pleural diseases, pleural effusion, pleural plaques, pneumococcal pneumonia, pneumoconioses (inorganic dust diseases), Pneumocystis carinii pneumonia, pneumocystosis, pneumonitis, pneumothorax, precapillary pulmonary
- 15 hypertension, primary (childhood) tuberculosis, primary (idiopathic) pulmonary hypertension, primary mesothelial neoplasms, primary pulmonary hypertension, progressive massive fibrosis, psittacosis, pulmonary actinomycosis, pulmonary air-leak syndromes, pulmonary alveolar proteinosis, pulmonary arteriovenous malformation, pulmonary blastoma, pulmonary capillary hemangiomatosis, pulmonary carcinosarcoma,
- 20 pulmonary edema, pulmonary embolism, pulmonary eosinophilia, pulmonary fibrosis, pulmonary hypertension, pulmonary hypoplasia, pulmonary infarction, pulmonary infiltration and eosinophilia, pulmonary interstitial air (pulmonary interstitial emphysema), pulmonary lesions, pulmonary nocardiosis, pulmonary parenchymal anomalies, pulmonary thromboembolism, pulmonary tuberculosis, pulmonary vascular disorders, pulmonary
- 25 vasculitides, pulmonary veno-occlusive disease, pyothorax, radiation pneumonitis, recurrent pulmonary emboli, red hepatization, respiration failure, respiratory syncytial virus, Reye's syndrome, rheumatoid lung disease, Rickettsial pneumonia, rupture of pulmonary arteries, sarcoidosis, scar cancer, scimitar syndrome, scleroderma, sclerosing hemangioma, secondary (adult) tuberculosis, secondary bacterial pneumonia, secondary pleural
- 30 neoplasms, secondary pulmonary hypertension, senile emphysema, siderosis, silicate

pneumoconiosis asbestosis, silicatosi, silicosis, simple nodular silicosis, Sjögren's syndrome, small airway lesions, small cell carcinoma, small cell undifferentiated (oat cell) carcinoma, spontaneous pneumothorax, sporotrichosis, sputum production, squamous (epidermoid) carcinoma, stannosis, staphylococcal pneumonia, suppuration (abscess formation), systemic lupus erythematosus, talcosi, tension pneumothorax, tracheal agenesis, tracheal stenosis, tracheobronchial amyloidosis, tracheobronchomegaly, tracheoesophageal fistula, transient tachypnea of the newborn (neonatal wet lung), tungsten carbide pneumoconiosis, usual interstitial pneumonia, usual interstitial pneumonitis, varicella, viral pneumonia, visceral pleural thickening, Wegener's granulomatosis, and whooping cough (pertussis).

Muscle. GPCRs expressed in the muscle are listed in Table 22. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the muscle. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a muscular disease or disorder, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 22. GPCRs Expressed in the Muscle

| | | | | | |
|---------|--------|---------|----------|--------|----------|
| ADMR | CRHR2 | GPR19 | GPR82 | MRGD | PGR4 |
| ADORA2B | CXCR4 | GPR2 | GPR9 | NMU2R | PGR5 |
| ADRA2B | CXCR6 | GPR21 | GPRC5C | NTSR1 | PGR7 |
| ADRB2 | EDG1 | GPR24 | GRCA | P2RY12 | PNR |
| AGR9 | EDG2 | GPR37L1 | GRPR | P2RY6 | RE2 |
| AGTRL1 | EDG7 | GPR39 | HGPCR19 | P2Y10 | TEM5 |
| CCR1 | EDNRA | GPR4 | HM74 | P2Y5 | TM7SF1 |
| CCR3 | EMR1 | GPR43 | HRH3 | PGR13 | TM7SF1L1 |
| CCR9 | FKSG79 | GPR48 | HTR4 | PGR15 | TM7SF1L2 |
| CCRL1 | FY | GPR55 | IL8RA | PGR16 | TM7SF3 |
| CD97 | FZD4 | GPR66 | KIAA0758 | PGR21 | TPRA40 |
| CELSR1 | FZD7 | GPR77 | LEC1 | PGR25 | TSHR |
| CMKLR1 | FZD8 | GPR80 | LEC2 | PGR26 | VIPR2 |
| CNR2 | GABBR1 | GPR81 | MRG | PGR27 | |

Exemplary diseases and disorders involving the muscles include abnormalities of ion channel closure, acetylcholine receptor deficiency, acetylcholinesterase deficiency, acid maltase deficiencies (type 2 glycogenosis), acquired myopathies, acquired myotonia, adult myotonic dystrophy, alveolar rhabdomyosarcoma, aminoglycoside drugs, amyloidosis, amyotrophic lateral sclerosis, antimyelin antibodies, bacteremic myositis, Batten's disease (neuronal ceroid lipofuscinoses), Becker's muscular dystrophy, benign neoplasms, Bornholm disease, botulism, branching enzyme deficiency (type 4 glycogenosis), carbohydrate storage diseases, carnitine deficiencies, carnitine palmitoyltransferase deficiency, central core disease, centronuclear (myotubular) myopathy, Chagas' disease, chondrodystrophic myotonia, chronic renal disease, congenital fiber type disproportion, congenital muscular dystrophy, congenital myopathies, congenital myotonic dystrophy, congenital paucity of synaptic clefts, cysticercosis, cytoplasmic body myopathy, debranching enzyme deficiency (type 3 glycogenosis), defect in acetylcholine synthesis, denervation, dermatomyositis, diabetes mellitus, diphtheria, disorders of glycolysis, disorders of neuromuscular junction, distal muscular dystrophy, drug induced inflammatory myopathy, Duchenne muscular dystrophy, embryonal rhabdomyosarcoma, Emery-Dreifuss muscular dystrophy, exotoxic bacterial infections, facioscapulohumeral muscular dystrophy, failure of neuromuscular transmission, fiber necrosis, fibromyalgia, fingerprint body myopathy, Forbe's disease, gas gangrene, Guillain-Barré syndrome, inclusion body myositis, infantile spinal muscular atrophies, infectious myositis, inflammatory myopathies, influenza, Isaac's syndrome, ischemia, Kearns-Sayre syndrome, lactase dehydrogenase deficiency, Lambert-Eaton syndrome, Leigh's disease, leuknock outdystrophies, limb girdle muscular dystrophy, lipid storage myopathies, Luft's disease, lysosomal glycogen storage disease with normal acid maltase activity, malignant neoplasms, malignant hyperthermia, McArdle's disease, MELAS syndrome (mitochondrial myopathy, encephalopathy, lacticacidosis, and strokes), MERRF syndrome (myoclonus epilepsy with ragged-red fibers), metabolic myopathies, microfiber myopathy, mitochondrial myopathies, multicore disease (minicore disease), multisystem triglyceride storage disease, muscle wasting from diabetes, muscular dystrophies, myasthenia gravis, myasthenic syndrome (Eaton-Lambert syndrome), myoadenylate deaminase deficiency, myoglobinuria,

myopathies, myophosphorylase deficiency (type 5 glycogenosis), myositis, myositis ossificans, myotonia congenita, myotonic muscular dystrophy, nemaline myopathy, ocular muscular dystrophy, oculopharyngeal muscular dystrophy, paramyotonia, parasytic myopathies, periodic paralysis, peripheral neuropathies, phosphofructokinase deficiency (type 7 glycogenosis), phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, pleomorphic rhabdomyosarcoma, polymyositis, Pompe's disease, progressive muscular atrophy, progressive systemic sclerosis, reducing body myopathy, Refsum's disease, rhabdomyolysis, rhabdomyoma, rhabdomyosarcoma, sarcoidosis, sarcoma botryoides, sarcotubular myopathy, secondary congenital myopathies, slow channel syndrome, spasmodic torticollis, spheroid body myopathy, spinal muscular atrophy, steroid myopathy, stiff-person syndrome, systemic lupus erythematosus, Tauri's disease, tick paralysis, toxic myopathies, toxoplasmosis, trichinosis, trilaminar fiber myopathy, type 2 myofiber atrophy, typhoid fever, vasculitis, viral myositis, and zebra body myopathy.

Ovary. GPCRs expressed in the ovary are listed in Table 23. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability of the GPCR in the ovary. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of disease, the risk of developing a particular ovarian disease or disorder, or an appropriate therapeutic course.

Table 23. GPCRs Expressed in the Ovary

| | | | | | |
|-----------|----------|---------|---------|-----------|-------|
| ADCYAP1R1 | CELSR2 | FZD5 | GPR55 | HUMNP1Y20 | PGR22 |
| ADMR | CHRM1 | FZD6 | GPR62 | IL8RA | PGR23 |
| ADORA1 | CHRM3 | FZD7 | GPR63 | IL8RB | PGR25 |
| ADORA2A | CHRM4 | G2A | GPR64 | KIAA0758 | PGR26 |
| ADORA2B | CMKBR1L2 | GABBR1 | GPR65 | KIAA1828 | PGR27 |
| ADORA3 | CMKLR1 | GALR1 | GPR66 | LEC1 | PGR28 |
| ADRA1D | CNR1 | GALR2 | GPR7 | LEC2 | PGR4 |
| ADRA2A | CNR2 | GALR3 | GPR73 | LEC3 | PGR5 |
| ADRA2B | CRHR1 | GCGR | GPR73L1 | LGR6 | PGR7 |
| ADRA2C | CX3CR1 | GLP1R | GPR74 | LGR7 | PGR8 |
| ADRB1 | CXCR4 | GPCR150 | GPR75 | LHCGR | PTAFR |

| | | | | | |
|--------|----------|---------|---------|--------|----------|
| ADRB2 | CXCR6 | GPR1 | GPR81 | LTB4R | PTGDR |
| ADRB3 | CYSLT1 | GPR10 | GPR82 | LTB4R2 | PTGER1 |
| AGTR1 | CYSLT2 | GPR102 | GPR84 | MAS1 | PTGER2 |
| AGTR2 | DJ287G14 | GPR103 | GPR85 | MC2R | PTGER3 |
| AGTRL1 | DRD5 | GPR105 | GPR86 | MC5R | PTGER4 |
| AVPR1A | EBI2 | GPR12 | GPR87 | MRG | PTGFR |
| AVPR1B | EDG1 | GPR14 | GPR88 | MrgA1 | PTHR1 |
| AVPR2 | EDG2 | GPR17 | GPR9 | MRGE | RAI3 |
| BAI2 | EDG3 | GPR18 | GPR91 | MRGF | RDC1 |
| BAI3 | EDG4 | GPR19 | GPR92 | MrgG | RE2 |
| BDKRB1 | EDG5 | GPR2 | GPRC5B | NMU2R | RHO |
| BDKRB2 | EDG6 | GPR20 | GPRC5C | NTSR1 | RRH |
| BLR1 | EDG7 | GPR21 | GPRC6A | OA1 | SALPR |
| C3AR1 | EDG8 | GPR22 | GRCA | OPN3 | SCTR |
| C5R1 | EDNRA | GPR23 | GRM4 | OPN4 | SMOH |
| CALCRL | EDNRB | GPR24 | GRM6 | OPRD1 | SREB3 |
| CASR | EMR1 | GPR27 | GRM7 | OPRL1 | SSTR1 |
| CCBP2 | ETL | GPR30 | GRM8 | OXTR | SSTR2 |
| CCKAR | F2R | GPR31 | H963 | P2RY1 | SSTR3 |
| CCKBR | F2RL1 | GPR33 | HCRT2 | P2RY12 | SSTR4 |
| CCR1 | F2RL2 | GPR34 | HGPCR11 | P2RY2 | SSTR5 |
| CCR2 | F2RL3 | GPR35 | HGPCR19 | P2Y10 | TAR3 |
| CCR3 | FKSG79 | GPR37L1 | HGPCR2 | P2Y5 | TBXA2R |
| CCR4 | FLJ14454 | GPR39 | HM74 | PGR1 | TEM5 |
| CCR5 | FPR1 | GPR4 | HRH1 | PGR10 | TM7SF1 |
| CCR6 | FPR-RS2 | GPR43 | HRH2 | PGR13 | TM7SF1L1 |
| CCR7 | FSHR | GPR44 | HTR1B | PGR14 | TM7SF1L2 |
| CCR8 | FY | GPR45 | HTR1D | PGR15 | TM7SF3 |
| CCR9 | FZD1 | GPR48 | HTR2A | PGR16 | TPRA40 |
| CCRL1 | FZD10 | GPR49 | HTR2B | PGR18 | TRHR2 |
| CCXCR1 | FZD2 | GPR50 | HTR5A | PGR2 | TSHR |
| CD97 | FZD3 | GPR51 | HTR6 | PGR20 | VIPR2 |
| CELSR1 | FZD4 | GPR54 | HTR7 | PGR21 | VLGR1 |

Exemplary ovarian diseases and disorders include autoimmune oophoritis, brenner tumors, choriocarcinoma, clear cell adenocarcinoma, clear cell carcinoma, corpus luteal cysts, decidual reaction, dysgerminoma, embryonal carcinoma, endometrioid tumors, endometriosis, endometriotic cysts, epithelial inclusion cysts, fibrothecoma, follicular cysts, gonadoblastoma, granulosa-stroma cell tumors, granulosa-theca cell tumor, gynandroblastoma, hilum cell hyperplasia, luteal cysts, luteal hematomas, luteoma of pregnancy, massive ovarian edema, metastatic neoplasm, mixed germ cell tumors, monodermal tumors, mucinous tumors, neoplastic cysts, ovarian changes secondary to cytotoxic drugs and radiation, ovarian fibroma, polycystic ovary syndrome, pregnancy

- luteoma, premature follicle depletion, pseudomyxoma peritonei, resistant ovary, serous tumors, Sertoli-Leydig cell tumor, sex-cord tumor with annular tubules, steroid (lipid) cell tumor, stromal hyperplasia, stromal hyperthecosis, teratoma, theca lutein cysts, thecomas, transitional cell carcinoma, undifferentiated carcinoma, and yolk sac carcinoma
- 5 (endodermal sinus tumor).

Peripheral Blood Lymphocytes: GPCRs expressed in the lymphocytes are listed in Table 24. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in lymphocytes. These polypeptides, or

10 polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 24. GPCRs Expressed in Peripheral Blood Lymphocytes

15

| | | | | | |
|---------|----------|----------|--------|----------|----------|
| ADMR | CELSR2 | F2R | GPR31 | HGPCR19 | PGR27 |
| ADORA2A | CELSR3 | F2RL1 | GPR35 | HM74 | PGR4 |
| ADORA2B | CHRM3 | F2RL2 | GPR4 | HRH2 | PGR7 |
| ADORA3 | CHRM4 | F2RL3 | GPR40 | HTR2B | PGR8 |
| ADRB1 | CMKBR1L2 | FKSG79 | GPR43 | HTR7 | PTAFR |
| ADRB2 | CMKLR1 | FLJ14454 | GPR44 | IL8RA | PTGER1 |
| AGR9 | CNR2 | FPR1 | GPR48 | IL8RB | PTGER2 |
| AGTRL1 | CX3CR1 | FPR-RS2 | GPR55 | KIAA0758 | PTGER3 |
| AVPR2 | CXCR4 | FZD1 | GPR65 | LEC1 | PTGER4 |
| BAI2 | CXCR6 | FZD10 | GPR66 | LEC2 | PTGIR |
| BLR1 | CYSLT1 | FZD4 | GPR68 | LTB4R | RAI3 |
| C3AR1 | CYSLT2 | FZD5 | GPR73 | MC5R | RDC1 |
| C5R1 | DJ287G14 | FZD6 | GPR82 | MRG | SMOH |
| CCBP2 | EBI2 | FZD7 | GPR83 | MRGE | SSTR2 |
| CCR1 | EDG1 | G2A | GPR84 | OPN3 | SSTR4 |
| CCR2 | EDG2 | GABBR1 | GPR85 | P2RY1 | TBXA2R |
| CCR3 | EDG3 | GALR2 | GPR86 | P2RY12 | TEM5 |
| CCR4 | EDG4 | GALR3 | GPR9 | P2RY2 | TM7SF1 |
| CCR5 | EDG5 | GLP1R | GPR92 | P2RY6 | TM7SF1L1 |
| CCR6 | EDG6 | GPCR150 | GPRC5B | P2Y10 | TM7SF3 |
| CCR7 | EDG7 | GPR105 | GPRC5C | P2Y5 | TPRA40 |
| CCR8 | EDG8 | GPR18 | GRCA | PGR13 | |
| CCR9 | EDNRA | GPR19 | GRM4 | PGR16 | |
| CCXCR1 | EDNRB | GPR2 | GRM6 | PGR22 | |
| CD97 | EMR1 | GPR22 | GRPR | PGR23 | |

| | | | | | |
|--------|-----|-------|------|-------|--|
| CELSR1 | ETL | GPR27 | H963 | PGR26 | |
|--------|-----|-------|------|-------|--|

Exemplary blood diseases and disorders include abnormal hemoglobins, abnormalities in granulocyte count, abnormalities in lymphocyte count, abnormalities in monocyte count, abnormalities of blood platelets, abnormalities of platelet function, acanthocytosis, acquired neutropenia, acute granulocytic leukemia, acute idiopathic thrombocytopenic purpura, acute infections, acute lymphoblastic leukemia, acute lymphocytic leukemia, acute myeloblastic leukemia, acute myelocytic leukemia, acute myeloid leukemia, acute pyogenic bacterial infections, acute red cell aplasia, acute response to endotoxin, adult T-cell leukemia/lymphoma, afibrinogenemia, alpha thalassemia, altered affinity of hemoglobin for oxygen, amyloidosis, anemia, anemia due to acute blood loss, anemia due to chronic blood loss, anemia of chronic disease, anemia of chronic renal failure, anemias associated with enzyme deficiencies, anemias associated with erythrocyte cytoskeletal defects, anemias caused by inherited disorders of hemoglobin synthesis, angiogenic myeloid metaplasia, aplastic anemia, ataxia-telangiectasia, Auer rods, autoimmune hemolytic anemias, B-cell chronic lymphocytic leukemia, B-cell chronic lymphoproliferative disorders, Bernard-Soulier disease, beta thalassemia, Blackfan-Diamond disease, brucellosis, Burkitt's lymphoma, Chédiak-Higashi syndrome, cholera, chronic acquired pure red cell aplasia, chronic granulocytic leukemia, chronic granulomatous disease, chronic idiopathic myelofibrosis, chronic idiopathic thrombocytopenic purpura, chronic lymphocytic leukemia, chronic lymphoproliferative disorders, chronic myelocytic leukemia, chronic myelogenous leukemia, chronic myeloid leukemia, chronic myeloproliferative disorders, congenital dyserythropoietic anemias, congenital dysfibrinogenemia, congenital neutropenia, corticosteroids, cyclic neutropenia, cytoplasmic maturation defect, deficiency of coagulation factors, delta-beta thalassemia, diphtheria, disorders of blood coagulation, disseminated intravascular coagulation & fibrinolysis, Döhle bodies, drug & chemical-induced hemolysis, drug-induced thrombocytopenia, drugs that suppress granulopoiesis, E. coli, early preleukemic myeloid leukemia, eosinophilia, eosinophilic granuloma, erythrocyte enzyme deficiency, erythrocyte

- membrane defects, essential thrombocythemia, factor 7 deficiency, familial cyclic neutropenia, Felty's syndrome, fibrinolytic activity, folate antagonists, folic acid deficiency, Gaucher disease, Glanzmann's thrombasthenia, glucose-6-phosphate dehydrogenase deficiency, granulated T-cell lymphocyte leukemia, granulocytic sarcoma, granulocytosis,
- 5 Hageman trait, hairy cell leukemia (leukemic reticuloendotheliosis), Hand-Schüller-Christian disease, heavy-chain disease, hemoglobin C disease, hemoglobin constant spring, hemoglobin S, hemoglobinopathies, hemolysis caused by infectious agents, hemolytic anemia, hemolytic anemia secondary to mechanical erythrocyte destruction, hemolytic blood transfusion reactions, hemolytic disease of the newborn, hemophagocytic disorders,
- 10 hemophilia A, hemophilia B (Christmas disease, factor 9 deficiency, hepatitis, hereditary elliptocytosis, hereditary spherocytosis, heterozygous beta thalassemia (Cooley's trait), homozygous beta thalassemia (Cooley's anemia), hypereosinophilic syndrome, hypoxia, idiopathic cold hemagglutinin disease, idiopathic thrombocytopenic purpura, idiopathic warm autoimmune hemolytic anemia, immune drug induced hemolysis, immune-mediated
- 15 hemolytic anemias, immunodeficiency disease, infantile neutropenia (Knock outstmann), instability of the hemoglobin molecule, iron deficiency anemia, isoimmune hemolytic anemia, juvenile chronic myeloid leukemia, Langerhans cell histiocytosis, large granular lymphocyte leukemia, lazy leukknock outcyte syndrome, Letterer-Siwe disease, leukemias, leukemoid reaction, leukknock outerythroblastic anemia, lipid storage diseases,
- 20 lymphoblastosis, lymphocytopenia, lymphocytosis, lymphoma, lymphopenia, macroangiopathic hemolytic anemia, malaria, marrow aplasia, May-Hegglin anomaly, measles, megaloblastic anemia, metabolic diseases, microangiopathic hemolytic anemia, microcytic anemia, miliary tuberculosis, mixed phenotupe acute leukemia, monoclonal gammopathy of undetermined significance, monocytic leukemia, monocytosis,
- 25 mucopolysaccharidosis, multiple myeloma, myeloblastic luekemia, myelodysplastic syndromes, myelofibrosis (agnogenic myeloid metaplasia), myeloproliferative diseases, myelosclerosis, neonatal thrombocytopenic purpura, neoplasms of hematopoietic cells, neutropenia, neutrophil dysfunction syndromes, neutrophil leukknock outcytosis, neutrophilia, Niemann-Pick disease, nonimmune drug-induced hemolysis, normocytic
- 30 anemia, nuclear maturation defects, parahemophilia, paroxysmal cold hemoglominuria,

paroxysmal nocturnal hemoglobinuria, Pelger-Huet anomaly, pernicious (Addisonian) anemia, plasma cell leukemia, plasma cell neoplasia, polycythemia, polycythemia rubra vera, presence of circulating anticoagulants, primary (idiopathic) thrombocythemia, primary neoplasms, prolymphocytic leukemia, Proteus, Pseudomonas, pure red cell aplasia,

5 pyogenic bacterial infection, pyruvate kinase deficiency, radiation, red cell aplasia, refractory anemias, rickettsial infections, Rosenthal's syndrome, secondary absolute polycythemia, septicemia, severe combined immunodeficiency disease, Sézary syndrome, sickle cell disease, sickle cell-beta thalassemia, sideroblastic anemia, solitary

10 plasmacytoma, storage pool disease, stress, structural hemoglobin variants, systemic lupus erythematosus, systemic mastocytosis, tart cell, T-cell chronic lymphoproliferative disorders, T-cell prolymphocytic leukemia, thalassemias, thrombocytopenia, thrombotic thrombocytopenic purpura, toxic granulation, toxic granules in severe infection, typhus, vitamin B12 deficiency, vitamin K deficiency, Von Willebrand's disease, Waldenstrom macroglobulinemia, and Wisknack outtt-aldrich syndrome.

15

Prostate. GPCRs expressed in the prostate are listed in Table 25. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the prostate. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine,

20 e.g., the presence of a disease or disorder involving the prostate, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 25. GPCRs Expressed in the Prostate

| | | | | | |
|-----------|----------|----------|---------|------------|-------|
| ADCYAP1R1 | CELSR1 | FKSG79 | GPR35 | HTR2B | PGR18 |
| ADMR | CELSR2 | FLJ14454 | GPR37L1 | HTR4 | PGR19 |
| ADORA1 | CELSR3 | FPR1 | GPR39 | HTR5A | PGR20 |
| ADORA2A | CHRM1 | FPR-RS2 | GPR4 | HTR7 | PGR21 |
| ADRA1A | CHRM2 | FY | GPR41 | HUMNP1IY20 | PGR22 |
| ADRA1D | CHRM3 | FZD1 | GPR43 | KIAA0758 | PGR25 |
| ADRA2A | CHRM4 | FZD10 | GPR48 | KIAA1828 | PGR26 |
| ADRA2B | CMKBR1L2 | FZD2 | GPR49 | LEC1 | PGR27 |
| ADRB1 | CMKLR1 | FZD3 | GPR54 | LEC2 | PGR4 |
| ADRB2 | CNR1 | FZD4 | GPR58 | LEC3 | PGR5 |

| | | | | | |
|--------|----------|---------|---------|--------|----------|
| AGR9 | CNR2 | FZD5 | GPR62 | LTB4R2 | PTAFR |
| AGTR1 | CRHR2 | FZD6 | GPR63 | MC2R | PTGDR |
| AGTR2 | CX3CR1 | FZD7 | GPR65 | MC3R | PTGER1 |
| AGTRL1 | CXCR4 | G2A | GPR73 | MC4R | PTGER3 |
| AVPR1B | CXCR6 | GABBR1 | GPR73L1 | MRG | PTGER4 |
| AVPR2 | CYSLT1 | GHSR | GPR80 | MRGE | PTGFR |
| BDKRB1 | CYSLT2 | GLP1R | GPR81 | MRGF | RAI3 |
| BDKRB2 | DJ287G14 | GPCR150 | GPR82 | MTNR1A | RDC1 |
| C3AR1 | EBI2 | GPR1 | GPR84 | MTNR1B | RE2 |
| C5R1 | EDG1 | GPR10 | GPR86 | NMU2R | SMOH |
| CALCRL | EDG2 | GPR102 | GPR9 | NPY6R | SSTR3 |
| CCKAR | EDG3 | GPR105 | GPR92 | OPN1SW | SSTR4 |
| CCR1 | EDG5 | GPR12 | GPRC5B | OPN3 | TAR2 |
| CCR2 | EDG6 | GPR14 | GPRC5C | OPRL1 | TAR4 |
| CCR3 | EDG7 | GPR18 | GPRC6A | OPRM1 | TEM5 |
| CCR4 | EDG8 | GPR2 | GRCA | P2RY2 | TM7SF1 |
| CCR5 | EDNRA | GPR21 | GRM6 | P2RY6 | TM7SF1L1 |
| CCR6 | EDNRB | GPR22 | H963 | P2Y10 | TM7SF3 |
| CCR7 | EMR1 | GPR23 | HCRT1 | P2Y5 | TPRA40 |
| CCR8 | ETL | GPR24 | HM74 | PGR10 | TRHR2 |
| CCR9 | F2R | GPR27 | HRH2 | PGR11 | TSHR |
| CCRL1 | F2RL1 | GPR30 | HRH3 | PGR12 | VIPR1 |
| CCXCR1 | F2RL2 | GPR31 | HTR1F | PGR13 | VIPR2 |
| CD97 | F2RL3 | GPR34 | HTR2A | PGR15 | |

- Exemplary diseases and disorders involving the prostate include acute bacterial prostatitis, acute prostatitis, adenoid basal cell tumor (adenoid cystic-like tumor), allergic
- 5 (eosinophilic) granulomatous prostatitis, atrophy, atypical adenomatous hyperplasia, atypical basal cell hyperplasia, basal cell adenoma, basal cell hyperplasia, BCG-induced granulomatous prostatitis, benign prostatic hyperplasia, benign prostatic hypertrophy, blue nevus, carcinosarcoma, chronic abacterial prostatitis, chronic bacterial prostatitis, cribriform hyperplasia, ductal (endometrioid) adenocarcinoma, granulomatous prostatitis, hematuria,
- 10 iatrogenic granulomatous prostatitis, idiopathic (nonspecific) granulous prostatitis, impotence, infectious granulomatous prostatitis, inflammatory pseudotumor, leiomyosarcoma, leukemia, lymphoepithelioma-like carcinoma, malaknock outplakia, malignant lymphoma, mucinous (colloid) carcinoma, nodular hyperplasia (benign prostatic hyperplasia), nonbacterial prostatitis, obstruction of urinary outflow, phyllodes tumor,
- 15 postatrophic hyperplasia, postirradiation granulomatous prostatitis, postoperative spindle cell nodules, postsurgical granulomatous prostatitis, prostatic adenocarcinoma, prostatic

carcinoma, prostatic intraepithelial neoplasia, prostatic melanosis, prostatic neoplasm, prostatitis, rhabdomyosarcoma, sarcomatoid carcinoma of the prostate, sclerosing adenosis, signet ring cell carcinoma, small-cell, undifferentiated carcinoma (high-grade neuroendocrine carcinoma), squamous cell carcinoma of the prostate, stromal hyperplasia with atypia, transitional cell carcinoma of the prostate, xanthogranulomatous prostatitis, and xanthoma.

Skin. GPCRs expressed in the skin are listed in Table 26. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the skin. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of skin disease or disorder, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 26. GPCRs Expressed in the Skin

| | | | | | |
|-----------|----------|---------|---------|----------|--------|
| ADCYAP1R1 | CCXCR1 | FPR1 | GPR44 | IL8RA | PGR20 |
| ADMR | CD97 | FSHR | GPR48 | KIAA0758 | PGR21 |
| ADORA1 | CELSR1 | FY | GPR49 | LEC1 | PGR22 |
| ADORA2A | CELSR2 | FZD1 | GPR50 | LEC2 | PGR25 |
| ADORA2B | CELSR3 | FZD10 | GPR54 | LEC3 | PGR26 |
| ADORA3 | CHRM1 | FZD2 | GPR64 | LGR6 | PGR27 |
| ADRA1A | CHRM3 | FZD3 | GPR65 | LTB4R | PGR4 |
| ADRA1D | CHRM4 | FZD4 | GPR68 | LTB4R2 | PTAFR |
| ADRA2A | CHRM5 | FZD5 | GPR7 | MAS1 | PTGDR |
| ADRA2B | CMKLR1 | FZD6 | GPR73 | MC1R | PTGER1 |
| ADRB1 | CNR1 | FZD7 | GPR73L1 | MC2R | PTGER2 |
| ADRB2 | CNR2 | FZD9 | GPR77 | MC5R | PTGER3 |
| ADRB3 | CRHR1 | G2A | GPR81 | MRG | PTGER4 |
| AGR9 | CRHR2 | GABBR1 | GPR82 | MRGE | PTGFR |
| AGTR1 | CX3CR1 | GALR2 | GPR83 | MRGF | PTHR1 |
| AGTR2 | CXCR4 | GALR3 | GPR84 | MrgG | RDC1 |
| AGTRL1 | CXCR6 | GLP1R | GPR85 | MTNR1B | RE2 |
| AVPR2 | CYSLT1 | GPCR150 | GPR86 | NPY1R | RRH |
| BAI2 | DJ287G14 | GPR1 | GPR87 | NTSR2 | SCTR |
| BAI3 | EBI2 | GPR105 | GPR9 | OA1 | SMOH |
| BDKRB1 | EDG1 | GPR14 | GPR91 | OPN3 | SREB3 |
| BLR1 | EDG2 | GPR18 | GPR92 | OPN4 | SSTR2 |
| C3AR1 | EDG3 | GPR19 | GPRC5B | OPRD1 | SSTR4 |

| | | | | | |
|--------|----------|-------|------------|--------|----------|
| C5R1 | EDG4 | GPR2 | GPRC5C | OXTR | TACR1 |
| CALCRL | EDG5 | GPR21 | GPRC5D | P2RY1 | TBXA2R |
| CASR | EDG6 | GPR22 | GRCA | P2RY12 | TEM5 |
| CCBP2 | EDG7 | GPR23 | GRM4 | P2RY2 | TM7SF1 |
| CCKBR | EDG8 | GPR27 | GRM8 | P2RY4 | TM7SF1L1 |
| CCR1 | EDNRA | GPR30 | H963 | P2RY6 | TM7SF1L2 |
| CCR2 | EDNRB | GPR31 | HCRTR2 | P2Y10 | TM7SF3 |
| CCR4 | EMR1 | GPR33 | HM74 | P2Y5 | TPRA40 |
| CCR5 | ETL | GPR34 | HRH1 | PGR1 | TRHR2 |
| CCR6 | F2R | GPR35 | HRH2 | PGR13 | TSHR |
| CCR7 | F2RL1 | GPR4 | HRH4 | PGR15 | VIPR1 |
| CCR8 | F2RL2 | GPR40 | HTR1D | PGR16 | VLGR1 |
| CCR9 | FKSG79 | GPR41 | HTR2B | PGR18 | |
| CCRL1 | FLJ14454 | GPR43 | HUMNPIIY20 | PGR19 | |

- Exemplary skin diseases and disorders include acanthosis nigricans, acne vulgaris, acquired epidermolysis bullosa, acrochordons, acrodermatitis enteropathica, acropustulosis,
- 5 actinic keratosis, acute cutaneous lupus erythematosus, age spots, allergic dermatitis, alopecia areata, angioedema, angiokeratoma, angioma, anthrax, apocrine tumors, arthropid-bite reactions, atopic dermatitis, atypical fibroxanthoma, Bart's syndrome, basal cell carcinoma (basal cell epithelioma), Bateman's purpura, benign familial pemphigus (Hailey-Hailey disease), benign keratoses, Berloque dermatitis, blue nevus, borderline leprosy,
- 10 Borrelia infection (lyme disease), Bowen's disease (carcinoma in situ), bullous pemphigoid, Café-au-lait spot, calcification, cellular blue nevus, cellulitis, Chagas' disease, chickenpox (varicella), chloasma, chondrodermatitis nodularis helices, chondroid syringoma, chronic actinic dermatitis, chronic cutaneous lupus erythematosus, chronic discoid lesions, cicatricial pemphigoid, collagen abnormalities, compound melanocytic nevus, congenital
- 15 melanocytic nevus, connective tissue nevus, contact dermatitis, cutaneous leishmaniasis, cutis laxa, cysts of the skin, dandruff, Darier's disease (keratosis follicularis), deep fungal infections, delayed-hypersensitivity reaction, dermal Spitz's nevus, dermatitis, dermatitis herpetiformis, dermatofibroma (cutaneous fibrous histiocytoma), dermatofibrosarcoma protuberans, dermatomyositis, dermatophyte infections, dermatophytid reactions, dermoid
- 20 cyst, dermatropic rickettsial infections, dermatropic viral infections, desmoplastic melanoma, discoid lupus erythematosus, dominant dystrophic epidermolysis bullosa, Dowling-Meara epidermolysis bullosa, dyshidrotic dermatitis, dysplastic nevi, eccrine

tumors, ecthyma, eczema, elastic tissue abnormalities, elastosis perforans serpiginosa, eosinophilic fasciitis, eosinophilic folliculitis, ephelides (freckles), epidermal cysts, epidermolysis bullosa, epidermolysis bullosa simplex, epidermotropic T-cell lymphoma, epidermotropic viruses, erysipelas, erythema multiforme, erythema nodosum, erythema nodosum leprosum, fibrotic disorders, fibrous tumors, follicular mucinosis, Fordyce's condition, fungal infections, genodermatoses, graft-versus-host disease, granuloma annulare, granulomatous vasculitis, Grover's disease, hair follicle infections, hair follicle tumors, hair loss, halo nevus, herpes simplex, herpes zoster (shingles), hidradenitis suppurativa, histiocytic lesions, HIV infections, hives, human papilloma virus, hyperhydrosis, ichthyosis, idiopathic skin diseases, impetigo, incontinentia pigmenti, intraepidermal spongiotic vesicles and bullae, invasive malignant melanoma, invasive squamous cell carcinoma, junctional epidermolysis bullosa, junctional melanocytic nevus, juvenile xanthogranuloma, Kaposi's sarcoma, keloids, keratinocytic lesions, keratinocytic tumors, keratoacanthoma, keratoderma blennorrhagicum, keratosis pilaris, leiomyoma, lentigo, lentigo maligna (Hutchinson's freckle), lepromatous leprosy, leprosy (Hansen's disease), leukocytoclastic vasculitis, lichen planus, lichen sclerosus et atrophicus, lichen simplex chronicus, lichen striatus, lichenoid disorders, lichenoid drug reactions, light eruptions, linear bullous IgA dermatitis, lipoma, Lucio's phenomenon, lupus erythematosus, lymphatic filariasis, lymphocytic vasculitis, lymphocytoma cutis, lymphoid lesions, lymphomatoid papulosis, malignant blue nevus, malignant lymphomas, malignant melanoma, malignant melanoma in situ (noninvasive malignant melanoma), mast cell neoplasms, mastocytosis, measles, melanocyte disorders, melanocytic lesions, melanocytic neoplasms, melanocytic nevus, melanocytic nevus with dysplasia, melanotic macule, reactive type, melasma, merkel cell (neuroendocrine) carcinoma, metastatic melanoma, miliaria, mixed connective tissue disease, molluscum contagiosum, morphea, mucin deposition, mucocutaneous leishmaniasis, mycetoma, mycobacterial infection, Mycobacterium marinum, Mycobacterium ulcerans, mycosis fungoides (cutaneous T cell lymphoma), myxoid cyst, necrobiosis lipoidica, necrobiosis lipoidica diabetorum, necrolytic migratory erythema, necrotizing fasciitis, neoplasms of dermal mesenchymal cells, neoplasms of keratinocytes, neoplasms of skin appendages, neoplasms of the

epidermis, neural tumors, neuroendocrine carcinoma of the skin, neurothekeoma, nevocellular nevus (melanocytic nevus), nummular dermatitis, obliterative vasculitis, onchocerciasis, Paget's disease, pale cell acanthoma of Degos, palisaded encapsulated neuroma, papillomavirus infections, paraneoplastic pemphigus, parasitic infections, pemphigoid gestationis, pemphigus, pemphigus foliaceus, pemphigus vulgaris, perivascular infiltrates, pilar cysts, pinta, pityriasis alba, pityriasis lichenoides chronica (of Juliusberg), pityriasis lichenoides et varioliformis acuta, pityriasis rosea, pityriasis rubra pilaris, plantar warts, porokeratosis, pressure necrosis, progressive systemic sclerosis, protozoal infections, pruritic urticarial papules and plaques of pregnancy, pruritis ani, pseudofolliculitis barbae, pseudoxanthoma elasticum, psoriasis vulgaris, pyogenic granuloma, radial growth type phase melanoma, recessive dystrophic epidermolysis bullosa, Reiter's syndrome, ringworm, Rochalimaea henselae infection, rosacea, rubella, sarcoidosis, scabies, Schamberg's disease, scleroderma, sebaceous hyperplasia, sebaceous tumors, seborrheic dermatitis, seborrheic keratosis, Sézary syndrome, skin manifestations of systemic diseases, small plaque parapsoriasis, smallpox (variola), solitary mastocytoma, spirochetal infections, Spitz's nevus, Spitz's nevus junctional type, squamous cell carcinoma, stasis dermatitis, Stevens-Johnson syndrome, subacute cutaneous lupus erythematosus, subcorneal pustular dermatosis, superficial fungal infections, superficial spreading melanoma in situ, syphilis, syringoma, systemic lupus erythematosus, systemic mastocytosis, tinea (dermatophytosis), tinea versicolor, toxic epidermal necrolysis, transient acantholytic dermatosis, tuberculoid leprosy, tuberculosis, urticaria, urticaria pigmentosa, urticarial vasculitis, vascular tumors, verruca vulgaris (common wart), vertical growth type phase melanoma, visceral leishmaniasis, vitiligo, warty dyskeratoma, Weber-Cockayne epidermolysis bullosa, Worringer-Knorr outcrop disease, xanthomas, xeroderma pigmentosum, xerosis, and yaws.

25

Spleen. GPCRs expressed in the spleen are listed in Table 27. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the spleen. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the spleen, the risk of developing a particular

30

disease or disorder, or an appropriate therapeutic course.

Table 27. GPCRs Expressed in the Spleen

| | | | | | |
|---------|----------|---------|--------|----------|----------|
| ADMR | CCRL1 | EMR1 | GPR34 | HRH2 | PGR26 |
| ADORA2A | CD97 | ETL | GPR35 | HTR2B | PGR27 |
| ADRB1 | CELSR1 | F2R | GPR4 | HTR7 | PGR7 |
| ADRB2 | CMKBR1L2 | F2RL2 | GPR43 | IL8RA | PTAFR |
| AGTR1 | CMKLR1 | F2RL3 | GPR65 | KIAA0758 | PTGER3 |
| BAI2 | CNR1 | FKSG79 | GPR82 | LTB4R | PTGER4 |
| BLR1 | CNR2 | FPR1 | GPR83 | MRG | PTGIR |
| C5R1 | CX3CR1 | FPR-RS2 | GPR84 | MRGE | RDC1 |
| CALCRL | CXCR4 | FY | GPR85 | OPN3 | SMOH |
| CCBP2 | CXCR6 | G2A | GPR86 | P2RY1 | SSTR2 |
| CCKAR | DJ287G14 | GABBR1 | GPR9 | P2RY12 | SSTR4 |
| CCR1 | EBI2 | GLP1R | GPR91 | P2RY2 | TBXA2R |
| CCR2 | EDG1 | GPR10 | GPR92 | P2RY6 | TM7SF1 |
| CCR3 | EDG2 | GPR105 | GPRC5B | P2Y10 | TM7SF1L1 |
| CCR5 | EDG3 | GPR15 | GRCA | P2Y5 | TM7SF3 |
| CCR6 | EDG5 | GPR18 | GRPR | PGR13 | TPRA40 |
| CCR7 | EDG6 | GPR19 | H963 | PGR16 | |
| CCR8 | EDG7 | GPR21 | HM74 | PGR18 | |
| CCR9 | EDG8 | GPR31 | HRH1 | PGR22 | |

5

Exemplary diseases and disorders of the spleen include abnormal immunoblastic proliferations of unknown origin, acute infections, acute parasitemias, agnogenic myeloid metaplasia, amyloidosis, angioimmunoblastic lymphadenopathy, antibody-coated cells, asplenia, autoimmune diseases, autoimmune hemolytic anemias, B-cell chronic lymphocytic leukemia and prolymphocytic leukemia, babesiosis, bone marrow involvement by carcinoma, brucellosis, carcinoma, ceroid histiocytosis, chronic alcoholism, chronic granulomatous disease, chronic hemolytic anemias, chronic hemolytic disorders, chronic immunologic inflammatory disorders, chronic infections, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic parasitemias, chronic uremia, cirrhosis, cold agglutinin disease, congestive splenomegaly, cryoglobulinemia, disseminated tuberculosis, dysproteinemias, endocrine disorders, erythroblastic leukemia, erythropoiesis, essential thrombocythemia, extramedullary hematopoiesis, Felty syndrome, fibrocongestive splenomegaly, fungal infections, gamm heavy-chain disease, Gaucher's disease, graft

- rejection, granulomatous infiltration, hairy cell leukemia, hamartomas, Hand-Schüller-Christian disease, hemangiomas, hemangiosarcomas, hematologic disorders, hemoglobinopathies, hemolytic anemias, hereditary elliptocytosis, hereditary spherocytosis, histiocytic medullary reticulosis, histiocytosis X, Hodgkin's disease, hypersensitivity
- 5 reactions, hypersplenism, hyposplenism, idiopathic thrombocytopenic purpura, IgA deficiency, immune granulomas, immune thrombocytopenia, immune thrombocytopenic purpura, immunodeficiency disorders, infection associated hemophagocytic syndrome, infectious granulomas, infectious mononucleosis, infective endocarditis, infiltrative splenomegaly, inflammatory pseudotumors, leishmaniasis, Leterer-Siwe disease, leukemia,
- 10 lipogranulomas, lymphocytic leukemias, lymphoma, malabsorption syndromes, malaria, malignant lymphoma, megakaryoblastic leukemia, metastatic tumor, monocytic leukemias, mucopolysaccharidoses, multicentric Castleman's disease, multiple myeloma, myelocytic leukemias, myelofibrosis, myeloproliferative syndromes, neoplasms, Niemann-Pick disease, non-Hodgkin's lymphoma, parasitic disorders, parasitized red blood cells, peliosis,
- 15 polycythemia rubra vera, portal vein congestion, portal vein stenosis, portal vein thrombosis, portal venous hypertension, rheumatoid arthritis, right-sided cardiac failure, sarcoidosis, sarcoma, secondary amyloidosis, secondary myeloid metaplasia, serum sickness, sickle-cell disease, splenic cysts, splenic infarction, splenic vein hypertension, splenic vein stenosis, splenic vein thrombosis, splenomegaly, storage diseases, systemic
- 20 lupus erythematosus, systemic vasculitides, T-cell chronic lymphocytic leukemia, thalassemia, thrombocytopenic purpura, thyrotoxicosis, trapping of immature hematologic cells, tuberculosis, tumorlike conditions, typhoid fever, vascular tumors, vasculitis, and viral infections.
- 25 *Stomach.* GPCRs expressed in the stomach are listed in Table 28. These receptors are thus potential targets for therapeutic compounds that may modulate the activity, expression, or stability in the stomach. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the stomach, the risk of developing a particular
- 30 disease or disorder, or an appropriate therapeutic course.

Table 28. GPCRs Expressed in the Stomach

| | | | | | |
|---------|----------|---------|----------|--------|----------|
| ADORA1 | CMKBR1L2 | FZD5 | GPR64 | LGR6 | PTGDR |
| ADORA2A | CMKLR1 | FZD6 | GPR66 | LTB4R | PTGER1 |
| ADRA1B | CNR2 | FZD7 | GPR68 | LTB4R2 | PTGER2 |
| ADRA2A | CX3CR1 | FZD8 | GPR75 | MC2R | PTGER3 |
| ADRA2B | CXCR4 | G2A | GPR81 | MC5R | PTGER4 |
| ADRB1 | CXCR6 | GABBR1 | GPR82 | MRG | PTGFR |
| ADRB2 | CYSLT1 | GALR1 | GPR84 | MRGE | PTGIR |
| AGTR2 | CYSLT2 | GALR3 | GPR85 | MRGF | PTHR2 |
| AGTRL1 | DJ287G14 | GLP1R | GPR86 | MrgG | RAI3 |
| AVPR1A | DRD3 | GLP2R | GPR87 | NTSR1 | RDC1 |
| BDKRB1 | EBI2 | GPCR150 | GPR91 | OPN3 | RE2 |
| BDKRB2 | EDG1 | GPR105 | GPR92 | OPRM1 | SALPR |
| BLR1 | EDG2 | GPR12 | GPRC5B | P2RY1 | SCTR |
| C3AR1 | EDG3 | GPR14 | GPRC5C | P2RY12 | SMOH |
| C5R1 | EDG4 | GPR18 | GRCA | P2RY2 | SSTR1 |
| CALCRL | EDG5 | GPR19 | GRM4 | P2RY4 | SSTR2 |
| CASR | EDG6 | GPR20 | H963 | P2RY6 | SSTR3 |
| CCBP2 | EDG7 | GPR21 | HCRT1 | P2Y10 | SSTR4 |
| CCKAR | EDG8 | GPR22 | HGPCR11 | P2Y5 | TACR1 |
| CCKBR | EDNRA | GPR23 | HGPCR19 | PGR13 | TACR2 |
| CCR1 | EDNRB | GPR24 | HM74 | PGR15 | TAR1 |
| CCR2 | EMR1 | GPR27 | HRH1 | PGR17 | TBXA2R |
| CCR5 | ETL | GPR30 | HRH2 | PGR18 | TEM5 |
| CCR6 | F2R | GPR35 | HRH4 | PGR20 | TM7SF1 |
| CCR8 | F2RL1 | GPR37 | HTR1B | PGR21 | TM7SF1L1 |
| CCR9 | F2RL2 | GPR37L1 | HTR1D | PGR22 | TM7SF3 |
| CCRL1 | FLJ14454 | GPR39 | HTR1F | PGR23 | TPRA40 |
| CCXCR1 | FPR1 | GPR4 | HTR2A | PGR25 | TRHR2 |
| CD97 | FPR-RS2 | GPR43 | HTR2B | PGR26 | TSHR |
| CELSR1 | FY | GPR45 | IL8RA | PGR27 | VIPR1 |
| CELSR2 | FZD1 | GPR48 | IL8RB | PGR4 | VIPR2 |
| CELSR3 | FZD10 | GPR49 | KIAA0758 | PGR5 | VLGR1 |
| CHRM2 | FZD2 | GPR54 | LEC1 | PGR7 | |
| CHRM3 | FZD3 | GPR55 | LEC2 | PGR8 | |
| CHRM4 | FZD4 | GPR63 | LEC3 | PTAFR | |

5

Exemplary diseases and disorders of the stomach include acute erosive gastropathy, acute gastric ulcers, adenocarcinomas, adenomas, adenomatous polyps, advanced gastric cancer, ampullary carcinoma, atrophic gastritis, bacterial gastritis, carcinoid tumors, carcinoma of the stomach, chemical gastritis, chronic (nonerosive) gastritis, chronic idiopathic gastritis, chronic nonatrophic gastritis, Chronkhite-Canada syndrome, congenital

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cysts, congenital diaphragmatic hernias, congenital diverticula, congenital duplications, congenital pyloric stenosis, congestive gastropathy, cyclic vomiting syndrome, decreased mucosal resistance to acid, diffuse or infiltrating adenocarcinoma, early gastric cancer, emphysematous gastritis, endocrine cell hyperplasia, environmental gastritis, eosinophilic

5 gastritis, eosinophilic gastroenteritis, epithelial polyps, erosive (acute) gastritis, fundic gland polyps, fungal gastritis, gangliocytic paragangliomas, gastric antral vascular ectasia, gastric adenocarcinoma, gastric outlet obstruction (pyloric stenosis), gastric ulcers, gastritis, gastroesophageal reflux, gastroparesis, granulomatous gastritis, *H. pylori* infection, hamartomatous polyps, heterotopias, heterotopic pancreatic tissue, heterotopic polyps,

10 hyperplastic gastropathy, hyperplastic polyps, hypersecretion of acid, infectious gastritis, inflammatory lesions of the stomach, inflammatory polyps, intestinal metaplasia, invasive carcinoma, ischemia, leiomyoma, linitis plastica, lumenally acting toxic chemicals, lymphocytic gastritis, lymphomas, malignant gastric stromal neoplasms, malignant lymphoma, malignant transformation of a benign gastric ulcer, Menentrier's disease

15 (hypertrophic gastritis, rugal hypertrophy), mesenchymal neoplasms, metastatic tumors, mucosal polyps, myoepithelial adenomas, myoepithelial hamartomas, neoplasms, neuroendocrine hyperplasias, neuroendocrine tumors, nonerosive gastritis and stomach cancer, nonneoplastic polyps, parasitic gastritis, peptic ulcer disease, phlegmonous gastritis, plasma cell gastritis, polypoid (fungating) adenocarcinoma, poorly differentiated

20 neuroendocrine carcinomas, precancerous lesions, Puetz-Jeghers syndrome, pyloric atresia, rapid gastric emptying, reflux of bile, stress ulcers, stromal tumors, superficial gastritis, type A chronic gastritis (autoimmune gastritis and pernicious anemia), type B chronic gastritis (chronic antral gastritis, *H. pylori* gastritis), ulcerating adenocarcinoma, vasculitis, viral gastritis, xanthomatous gastritis, and Zollinger-Ellison syndrome.

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Testes. GPCRs expressed in the testes are listed in Table 29. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability of the GPCR in the testes. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to

30 determine, e.g., the presence of a disease or disorder involving the testes, the risk of

developing a particular disease or disorder, or an appropriate therapeutic course.

Table 29. GPCRs Expressed in the Testes

| | | | | | |
|-----------|----------|---------|---------|------------|----------|
| ADCYAP1R1 | CHRM5 | GALR1 | GPR65 | HTR2B | PGR19 |
| ADMR | CMKLR1 | GALR3 | GPR66 | HTR4 | PGR2 |
| ADORA1 | CNR1 | GCGR | GPR68 | HTR5A | PGR20 |
| ADORA2A | CNR2 | GHRHR | GPR7 | HTR7 | PGR21 |
| ADORA2B | CRHR1 | GIPR | GPR73 | HUMNP1IY20 | PGR22 |
| ADORA3 | CRHR2 | GLP1R | GPR73L1 | IL8RA | PGR23 |
| ADRA1A | CX3CR1 | GLP2R | GPR74 | KIAA0758 | PGR25 |
| ADRA1D | CXCR4 | GPCR150 | GPR75 | KIAA1828 | PGR27 |
| ADRA2A | CXCR6 | GPR1 | GPR77 | LEC1 | PGR3 |
| ADRB1 | CYSLT1 | GPR10 | GPR80 | LEC2 | PGR4 |
| ADRB2 | DJ287G14 | GPR105 | GPR81 | LEC3 | PGR7 |
| AGR9 | DRD2 | GPR12 | GPR82 | LGR6 | PPYR1 |
| AGTR1 | DRD4 | GPR15 | GPR83 | LGR8 | PTAFR |
| AGTR2 | EBI2 | GPR18 | GPR84 | LHCGR | PTGDR |
| AGTRL1 | EDG1 | GPR19 | GPR85 | LTB4R2 | PTGER2 |
| AVPR1A | EDG2 | GPR2 | GPR86 | MAS1 | PTGER3 |
| BAI2 | EDG3 | GPR20 | GPR87 | MC2R | PTGER4 |
| BDKRB1 | EDG4 | GPR21 | GPR91 | MC3R | PTGFR |
| BDKRB2 | EDG5 | GPR22 | GPR92 | MC5R | PTGIR |
| BLR1 | EDG7 | GPR23 | GPRC5B | MGR | RAI3 |
| BRS3 | EDNRA | GPR24 | GPRC5C | MRGE | RDC1 |
| C3AR1 | EDNRB | GPR25 | GPRC5D | MGRF | RE2 |
| C5R1 | EMR1 | GPR3 | GPRC6A | MTNR1A | RHO |
| CALCRL | ETL | GPR30 | GRCA | NMBR | RRH |
| CASR | F2R | GPR31 | GRM2 | NPFF1R | SCTR |
| CCBP2 | F2RL1 | GPR34 | GRM4 | NPY1R | SMOH |
| CCKAR | F2RL2 | GPR35 | GRM5 | NPY6R | SSTR2 |
| CCKBR | FKSG79 | GPR37 | GRM6 | NTSR1 | SSTR3 |
| CCR1 | FLJ14454 | GPR37L1 | GRM7 | NTSR2 | SSTR5 |
| CCR2 | FPR1 | GPR39 | GRM8 | OPN1MW | TACR2 |
| CCR4 | FSHR | GPR4 | H963 | OPN3 | TAR3 |
| CCR5 | FY | GPR43 | HCRT1 | OPRL1 | TEM5 |
| CCR6 | FZD1 | GPR45 | HCRT2 | OPRM1 | TM7SF1 |
| CCR7 | FZD10 | GPR48 | HGPCR2 | OXTR | TM7SF1L1 |
| CCRL1 | FZD2 | GPR49 | HM74 | P2RY1 | TM7SF1L2 |
| CCXCR1 | FZD3 | GPR50 | HRH1 | P2RY12 | TM7SF3 |
| CD97 | FZD4 | GPR51 | HRH2 | P2RY2 | TPRA40 |
| CELSR1 | FZD5 | GPR54 | HRH3 | P2Y5 | TRHR2 |
| CELSR2 | FZD6 | GPR55 | HRH4 | PGR1 | TSHR |
| CELSR3 | FZD7 | GPR57 | HTR1A | PGR11 | VIPR2 |
| CHRM1 | FZD8 | GPR6 | HTR1B | PGR13 | VLGR1 |
| CHRM2 | FZD9 | GPR61 | HTR1D | PGR14 | |
| CHRM3 | G2A | GPR62 | HTR1F | PGR15 | |
| CHRM4 | GABBR1 | GPR63 | HTR2A | PGR17 | |

Exemplary diseases and disorders involving the testes include aberrant ducts of
 Haller, abnormal productions of hormones, abnormalities of testicular descent, acute
 5 epididymoorchitis, adenomatoid tumor, adenomatous hyperplasia of the rete testis,
 adenovirus, administration of estrogens, adrenal rests, alcoholic cirrhosis, amyloidosis,
 anorchism, appendix testes, bacterial infections, Brucella, cachexia, carcinoma in situ,
 carcinoma of the rete testis, chlamydia, choriocarcinoma, choristomas, chronic fibrosing
 epididymoorchitis, coxsackie virus B, cryptorchidism, cystic dysplasia of the rete testis,
 10 cytomegalovirus, dystopia, *E. coli* infection, Echinococcus granulosus, ectopic testes,
 embryonal carcinoma, epididymoorchitis, Fournier's scrotal gangrene, fungal infection,
 germ cell aplasia, germ cell neoplasms, gonadal dysgenesis, gonadal stromal neoplasms,
 granulomatous orchitis, granulosa cell tumors, Haemophilus influenzae, HIV,
 hypergonadism, hypogonadotropic hypogonadism, hypopituitarism, hypospermatogenesis,
 15 hydrocele, idiopathic granulomatous orchitis, incomplete maturation arrest, infarction,
 infertility, inflammatory diseases, inflammatory lesions, interstitial (Leydig) cell tumors,
 Klinefelter's syndrome, iatrogenic lesions, Leydig cell tumors, malaknock outplakia,
 malignant lymphoma, malnutrition, maturation arrest of spermatogenesis, metastatic
 tumors, mixed germ cell tumors, monorchism, mumps orchitis, mycobacteria, *Neisseria*
 20 *gonorrhoeae* infection, neoplasms, obstruction to outflow of semen, orchitis, parasitic
 infection, polyorchidism, radiation, Salmonella, sarcoidosis, *Schistosoma haematobium*
 infection, seminoma, Sertoli cell tumors, sex cord stromal tumors, sperm granuloma,
 spermatocytic seminoma, syphilis, teratocarcinoma, teratoma, testicular atrophy, testicular
 neoplasms, testicular torsion, *Treponema pallidum* infection, tuberculous
 25 epididymoorchitis, tumors of nonspecific stroma, undescended testes, uropathogens,
 varicocele, vascular disturbances, vasculitis, viral infection, *Wuchereria bancrofti* infection,
 and yolk sac carcinoma.

Thymus. GPCRs expressed in the thymus are listed in Table 30. These receptors are
 30 thus potential targets for therapeutic compounds that may modulate their activity,

expression, or stability in the thymus. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the thymus, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

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Table 30. GPCRs Expressed in the Thymus

| | | | | | |
|-----------|----------|---------|---------|----------|----------|
| ADCYAP1R1 | CCXCR1 | FKSG79 | GPR35 | HRH3 | PGR25 |
| ADMR | CD97 | FPR1 | GPR37 | HTR2B | PGR26 |
| ADORA1 | CELSR1 | FY | GPR37L1 | HTR7 | PGR27 |
| ADORA2A | CELSR2 | FZD1 | GPR4 | IL8RA | PGR4 |
| ADORA2B | CHRM1 | FZD10 | GPR43 | KIAA0758 | PGR7 |
| ADORA3 | CHRM2 | FZD2 | GPR48 | LEC1 | PTAFR |
| ADRA1A | CHRM3 | FZD3 | GPR57 | LEC2 | PTGER1 |
| ADRA1D | CMKBR1L2 | FZD4 | GPR63 | LEC3 | PTGER2 |
| ADRB1 | CMKLR1 | FZD5 | GPR65 | LTB4R2 | PTGER3 |
| ADRB2 | CNR2 | FZD6 | GPR66 | MC2R | PTGER4 |
| AGTR1 | CRHR2 | FZD7 | GPR73 | MC4R | PTGFR |
| AGTRL1 | CX3CR1 | FZD8 | GPR75 | MC5R | PTGIR |
| AVPR2 | CXCR4 | FZD9 | GPR81 | MRG | PTHR1 |
| BAI2 | CXCR6 | G2A | GPR83 | MRGE | RAI3 |
| BDKRB1 | CYSLT1 | GABBR1 | GPR84 | MRGF | RDC1 |
| BLR1 | DJ287G14 | GALR1 | GPR85 | MrgG | RE2 |
| C3AR1 | DRD3 | GHRHR | GPR86 | MTNR1A | SCTR |
| C5R1 | EBI2 | GLP1R | GPR9 | NTSR2 | SMOH |
| CALCRL | EDG1 | GPCR150 | GPR91 | OPN3 | SSTR2 |
| CCBP2 | EDG2 | GPR1 | GPR92 | P2RY1 | TBXA2R |
| CCKAR | EDG3 | GPR105 | GPRC5B | P2RY12 | TEM5 |
| CCKBR | EDG5 | GPR18 | GPRC5C | P2RY4 | TM7SF1 |
| CCR1 | EDG6 | GPR19 | GPRC5D | P2RY6 | TM7SF1L1 |
| CCR2 | EDNRA | GPR2 | GPRC6A | P2Y10 | TM7SF1L2 |
| CCR4 | EDNRB | GPR21 | GRCA | P2Y5 | TM7SF3 |
| CCR5 | EMR1 | GPR22 | GRM2 | PGR13 | TPRA40 |
| CCR6 | ETL | GPR23 | GRM4 | PGR15 | TRHR2 |
| CCR7 | F2R | GPR24 | GRPR | PGR16 | TSHR |
| CCR8 | F2RL1 | GPR27 | H963 | PGR20 | VIPR2 |
| CCR9 | F2RL2 | GPR30 | HM74 | PGR21 | |
| CCRL1 | F2RL3 | GPR31 | HRH2 | PGR22 | |

10 Exemplary diseases and disorders of the thymus include accidental involution, acute accidental involution, acute lymphoblastic leukemia of T cell type, agenesis, age-related involution, anaplastic carcinoma, ataxia telangiectasia, atrophy, bacterial infections,

bacterial mediastinitis, basaloid carcinoma, bone marrow transplantation, Bruton's agammaglobulinemia, carcinosarcoma, chronic accidental involution, clear cell carcinoma, cortical thymoma, cytomegalovirus, DiGeorge syndrome, dysgenesis, dysplasia with pattern similar to severe atrophy, dysplasia with pseudoglandular appearance, dysplasia with stromal conticomedullary differentiation, ectopia, germ cell tumors, Grave's disease, histiocytosis X, HIV, Hodgkin's disease, hyperplasia, infectious mononucleosis, involution, lymphoblastic lymphoma of T-cell type, lymphoepithelioma-like carcinoma, lymphofollicular thymitis, maldescent, malignant lymphomas, malignant thymoma, measles giant cell pneumonia, medullary thymoma, mixed (composite) thymoma, mucoepidermoid carcinoma, myasthenia gravis, neonatal syphilis, neoplasms, Omenn's syndrome, predominantly cortical (organoid) thymoma, primary mediastinal B-cell lymphoma of high-grade malignancy, sarcomatoid carcinoma, seminoma, severe combined immunodeficiency, short limb dwarfism, simple dysplasia, small cell carcinoma, small-cell B-cell lymphoma of MALT type, squamous cell carcinoma, systemic lupus erythematosus, teratoma, thymic carcinoid, thymic carcinoma, thymic cysts, thymic epithelial cysts, thymic epithelial tumorw, thymic neoplasms, thymitis with diffuse B-cell infiltrations, thymolipoma, thymoma, true thymic hyperplasia, varicella-zoster, viral infections, well differentiated thymic carcinoma, and Wiscott-Aldrich syndrome.

Thyroid. GPCRs expressed in the thyroid are listed in Table 31. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the thyroid. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the thyroid, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

Table 31. GPCRs Expressed in the Thyroid

| | | | | | |
|-----------|-------|------|-------|----------|-------|
| ADCYAP1R1 | CHRM1 | FZD3 | GPR64 | KIAA0758 | PGR21 |
| ADMR | CHRM2 | FZD4 | GPR65 | KIAA1828 | PGR22 |
| ADORA1 | CHRM3 | FZD5 | GPR66 | LEC1 | PGR23 |

| | | | | | |
|---------|----------|---------|---------|--------|----------|
| ADORA2A | CHRM4 | FZD6 | GPR73 | LEC2 | PGR25 |
| ADORA2B | CMKBR1L2 | FZD7 | GPR73L1 | LEC3 | PGR26 |
| ADORA3 | CMKLR1 | FZD9 | GPR74 | LGR6 | PGR27 |
| ADRA1A | CNR1 | G2A | GPR75 | LTB4R | PGR4 |
| ADRA1D | CNR2 | GABBR1 | GPR77 | LTB4R2 | PGR7 |
| ADRA2A | CRHR2 | GALR3 | GPR81 | MAS1 | PTAFR |
| ADRA2B | CX3CR1 | GIPR | GPR82 | MC2R | PTGDR |
| ADRB1 | CXCR4 | GLP1R | GPR83 | MC4R | PTGER1 |
| ADRB2 | CXCR6 | GPCR150 | GPR84 | MC5R | PTGER2 |
| AGR9 | CYSLT1 | GPR1 | GPR85 | MRG | PTGER3 |
| AGTR1 | CYSLT2 | GPR105 | GPR86 | MRGE | PTGER4 |
| AGTR2 | DJ287G14 | GPR12 | GPR87 | MRGF | PTGFR |
| AGTRL1 | DRD2 | GPR14 | GPR88 | MrgG | PTGIR |
| AVPR1A | DRD3 | GPR18 | GPR9 | MTNR1A | PTHR1 |
| AVPR2 | DRD4 | GPR19 | GPR90 | NPY1R | PTHR2 |
| BDKRB1 | EBI2 | GPR2 | GPR91 | NTSR2 | RAI3 |
| BDKRB2 | EDG1 | GPR20 | GPR92 | OPN1MW | RDC1 |
| BLR1 | EDG2 | GPR21 | GPRC5B | OPN3 | RE2 |
| C3AR1 | EDG3 | GPR22 | GPRC5C | OPN4 | RRH |
| C5R1 | EDG4 | GPR23 | GRCA | OPRM1 | SALPR |
| CALCRL | EDG5 | GPR24 | GRM4 | OXTR | SCTR |
| CASR | EDG6 | GPR27 | GRM6 | P2RY1 | SMOH |
| CCBP2 | EDG7 | GPR30 | GRM7 | P2RY12 | SSTR1 |
| CCKAR | EDG8 | GPR31 | H963 | P2RY2 | SSTR2 |
| CCR1 | EDNRA | GPR33 | HCTR2 | P2RY4 | SSTR4 |
| CCR2 | EDNRB | GPR34 | HGPCR11 | P2RY6 | TACR1 |
| CCR3 | EMR1 | GPR35 | HM74 | P2Y10 | TBXA2R |
| CCR4 | ETL | GPR37 | HRH1 | P2Y5 | TEM5 |
| CCR5 | F2R | GPR37L1 | HRH2 | PGR1 | TM7SF1 |
| CCR6 | F2RL1 | GPR39 | HRH3 | PGR11 | TM7SF1L1 |
| CCR7 | F2RL2 | GPR4 | HTR1B | PGR12 | TM7SF1L2 |
| CCR8 | F2RL3 | GPR41 | HTR1D | PGR13 | TM7SF3 |
| CCR9 | FKSG79 | GPR43 | HTR2A | PGR14 | TPRA40 |
| CCRL1 | FPR1 | GPR44 | HTR2B | PGR15 | TRHR2 |
| CCXCR1 | FPR-RS2 | GPR48 | HTR4 | PGR16 | TSHR |
| CD97 | FY | GPR49 | HTR5A | PGR18 | VIPR2 |
| CELSR1 | FZD1 | GPR54 | HTR7 | PGR19 | |
| CELSR2 | FZD10 | GPR62 | IL8RA | PGR2 | |
| CELSR3 | FZD2 | GPR63 | IL8RB | PGR20 | |

Exemplary diseases and disorders of the thyroid include aberrant thyroid glands, accessory thyroid glands, adenoma with bizarre nuclei, agenesis, amphotericin variant of medullary carcinoma, anaplastic (undifferentiated) carcinoma, aplasia, atrophic thyroiditis, atypical adenoma, autoimmune thyroiditis, carcinoma, C-cell hyperplasia, clear cell tumors, clear cell variant of medullary carcinoma, colloid adenoma, columnar variant of papillary

carcinoma, congenital hypothyroidism (cretinism), diffuse nontoxic goiter, diffuse sclerosing variant of papillary carcinoma, dys hormonogenic goiter, embryonal adenoma, encapsulated variant of papillary carcinoma, endemic cretinism, endemic goiter, enzyme deficiency, fetal adenoma, follicular adenoma, follicular carcinoma, follicular variant of medullary carcinoma, follicular variant of papillary carcinoma, fungal infection, giant cell variant of medullary carcinoma, goiter induced by antithyroid agents, goitrous hypothyroidism, Graves' disease, Hashimoto's autoimmune thyroiditis, Hürthle cell (oncocytic) adenoma, hyalinized trabecular adenoma, hyperthyroidism, hypothyroid cretinism, hypothyroidism, iodine deficiency, juvenile thyroiditis, iatrogenic hypothyroidism, lingual thyroid glands, malignant lymphoma, medullary carcinoma, melanocytic variant of medullary carcinoma, mesenchymal tumors, metastatic tumors, minimally invasive follicular carcinoma, mixed medullary and follicular carcinoma, mixed medullary and papillary carcinoma, mucinous carcinoma, mucoepidermoid carcinoma, multinodular goiter, myxedema, neoplasms, neurologic cretinism, nonspecific lymphocytic (simple chronic) thyroiditis, oncocytic variant of medullary carcinoma, palpation thyroiditis, papillary carcinoma, papillary microcarcinoma, papillary variant of medullary carcinoma, partial agenesis, pituitary thyrotropic adenoma, poorly differentiated carcinoma, primary hypothyroidism, pseudopapillary variant of medullary carcinoma, Riedel's thyroiditis, sclerosing mucoepidermoid carcinoma with eosinophilia, silent thyroiditis, simple adenoma, small cell variant of medullary carcinoma, solitary thyroid nodule, sporadic goiter, squamous cell carcinoma, squamous variant of medullary carcinoma, subacute thyroiditis (DeQuervain, granulomatous, giant cell thyroiditis), tall cell variant of papillary carcinoma, tertiary syphilis, thyroglossal duct cyst, thyroid agenesis, thyroid nodules, thyroiditis, thyrotoxicosis, toxic adenoma, toxic multinodular goiter, toxic nodular goiter (Plummer's disease), tuberculosis, tubular variant of medullary carcinoma, and widely invasive follicular carcinoma.

Uterus. GPCRs expressed in the uterus are listed in Table 32. These receptors are thus potential targets for therapeutic compounds that may modulate their activity, expression, or stability in the uterus. These polypeptides, or polymorphs of these

polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder of the uterus, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

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Table 32. GPCRs Expressed in the Uterus

| | | | | | |
|-----------|----------|---------|----------|--------|----------|
| ADCYAP1R1 | CHRM1 | FZD10 | GPR63 | LEC1 | PGR26 |
| ADMR | CHRM2 | FZD2 | GPR64 | LEC2 | PGR27 |
| ADORA1 | CHRM3 | FZD3 | GPR65 | LEC3 | PGR4 |
| ADORA2A | CHRM4 | FZD4 | GPR73 | LGR6 | PGR5 |
| ADORA2B | CMKBR1L2 | FZD5 | GPR73L1 | LGR7 | PGR7 |
| ADORA3 | CMKLR1 | FZD6 | GPR75 | LGR8 | PTAFR |
| ADRA1A | CNR1 | FZD7 | GPR77 | LHCGR | PTGDR |
| ADRA1D | CNR2 | G2A | GPR82 | LTB4R | PTGER1 |
| ADRA2A | CRHR2 | GABBR1 | GPR83 | LTB4R2 | PTGER2 |
| ADRB1 | CX3CR1 | GALR3 | GPR84 | MAS1 | PTGER3 |
| ADRB2 | CXCR4 | GLP1R | GPR85 | MC2R | PTGER4 |
| AGTR1 | CXCR6 | GPCR150 | GPR86 | MC5R | PTGFR |
| AGTR2 | CYSLT1 | GPR1 | GPR9 | MRG | PTGIR |
| AGTRL1 | DJ287G14 | GPR103 | GPR90 | MRGE | PTHR1 |
| AVPR1A | DRD3 | GPR105 | GPR91 | MRGF | RAI3 |
| AVPR2 | EBI2 | GPR18 | GPR92 | NMU2R | RDC1 |
| BAI2 | EDG1 | GPR19 | GPRC5B | NPY1R | RE2 |
| BDKRB1 | EDG2 | GPR20 | GPRC5C | OPN1MW | RRH |
| BDKRB2 | EDG3 | GPR21 | GRCA | OPN3 | SCTR |
| C3AR1 | EDG5 | GPR23 | GRM8 | OXTR | SMOH |
| C5R1 | EDG6 | GPR24 | H963 | P2RY1 | SREB3 |
| CALCRL | EDG7 | GPR27 | HCRTR2 | P2RY12 | SSTR2 |
| CASR | EDG8 | GPR30 | HGPCR11 | P2RY2 | SSTR4 |
| CCBP2 | EDNRA | GPR31 | HGPCR19 | P2RY6 | TACR1 |
| CCR1 | EDNRB | GPR33 | HGPCR2 | P2Y10 | TACR2 |
| CCR2 | EMR1 | GPR34 | HM74 | P2Y5 | TAR2 |
| CCR3 | ETL | GPR35 | HRH1 | PGR1 | TBXA2R |
| CCR4 | F2R | GPR37 | HRH2 | PGR10 | TEM5 |
| CCR5 | F2RL1 | GPR37L1 | HRH3 | PGR13 | TM7SF1 |
| CCR6 | F2RL2 | GPR39 | HRH4 | PGR15 | TM7SF1L1 |
| CCR7 | F2RL3 | GPR4 | HTR1D | PGR16 | TM7SF3 |
| CCR8 | FLJ14454 | GPR43 | HTR2A | PGR19 | TPRA40 |
| CCRL1 | FPR1 | GPR44 | HTR2B | PGR2 | TRHR2 |
| CCXCR1 | FPR-RS2 | GPR48 | HTR4 | PGR21 | TSHR |
| CD97 | FSHR | GPR49 | HTR7 | PGR22 | VIPR2 |
| CELSR1 | FY | GPR54 | IL8RA | PGR23 | |
| CELSR2 | FZD1 | GPR55 | KIAA0758 | PGR25 | |

Exemplary diseases and disorders of the uterus include acute cervicitis, acute

- endometritis, adenocanthoma, adenocarcinoma, adenocarcinoma in situ, adenoid cystic carcinoma, adenomatoid tumor, adenomyoma, adenomyosis (endometriosis interna), adenosquamous carcinoma, amebiasis, arias-Stella phenomenon, atrophy of the endometrium, atypical hyperplasia, benign polypoid lesions, benign stromal nodule,
- 5 carcinoid tumors, carcinoma in situ, cervical intraepithelial neoplasia, chlamydia, chronic cervicitis, chronic nonspecific endometritis, ciliated (tubal) metaplasia, clear cell adenocarcinoma, clear cell carcinoma, clear cell metaplasia, complex hyperplasia with atypia, complex hyperplasia without atypia, condyloma aduminatum, congenital abnormalities, corpus cancer syndrome, cystic hyperplasia, dysfunctional uterine bleeding,
- 10 dysmenorrhea, dysplasia of the cervix (cervical intraepithelial neoplasia, squamous intraepithelial lesion), endocervical adenocarcinoma, endocervical polyp, endolymphatic stromal myosis, endometrial adenocarcinoma, endometrial carcinoma, endometrial hyperplasia, endometrial polyps, endometrial stromal neoplasms, endometriosis, endometritis, endometroid (pure) adenocarcinoma of the endometrium, endometroid
- 15 adenocarcinoma with squamous differentiation, eosinophilic metaplasia, epimenorrhea, exogenous progestational hormone effect, extrauterine endometriosis (endometriosis externa), gestational trophoblastic disease, gonorrhea, hemangioma, herpes simplex virus type 2, high-grade squamous intraepithelial lesion, human papillomavirus, hyperplasia, inadequate luteal phase, infertility, inflammatory cervical lesions, inflammatory lesions of
- 20 the endometrium, intravenous leiomyomatosis, invasive carcinoma of cervix, invasive squamous cell carcinoma, leiomyoma, leiomyosarcoma, lipoma, low-grade squamous intraepithelial lesion, malignant mixed mesodermal (Müllerian) tumor, menorrhagia, metaplasia, metastasizing leiomyoma, metastatic carcinoma, microglandular hyperplasia, microinvasive carcinoma, microinvasive squamous cell carcinoma, mucinous
- 25 adenocarcinoma, mucinous metaplasia, neoplasms of the cervix, neoplasms of the endometrium, neoplasms of the myometrium, nonneoplastic cervical proliferations, papillary syncytial metaplasia, papilloma, pelvic inflammatory disease, peritoneal leiomyomatosis, persistent luteal phase, postmenopausal bleeding, serous papillary adenocarcinoma, simple hyperplasia with atypia, simple hyperplasia without atypia,
- 30 spontaneous abortion, squamous carcinoma, squamous cell neoplasia, squamous

intraepithelial lesions, squamous metaplasia, squamous metaplasia (acanthosis), stromal sarcoma, tuberculous endometritis, unopposed estrogen effect, uterine leiomyomata, verrucous carcinoma, vestigial and heterotopic structures, villoglandular papillary adenocarcinoma, and viral endometritis.

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Other GPCRs

Additional GPCRs are listed in Table 33. The expression data for these receptors is unknown, and they may be expressed anywhere in the body, for example, in any of the tissues described above. These receptors may be potential targets for therapeutic compounds that may modulate their activity, expression, or stability for the treatment of a disease or disorder involving such a receptor. These polypeptides, or polymorphs of these polypeptides, may form the basis of a therapeutic regimen, or a diagnostic test to determine, e.g., the presence of a disease or disorder, the risk of developing a particular disease or disorder, or an appropriate therapeutic course.

15

Table 33. GPCRs Without Expression Data

| | | | | | |
|--------|----------|---------|---------|---------|-------|
| GPR32 | GPR38 | F2RL | FPRL1 | FPRL2 | TA10 |
| TA11 | TA12 | TA14 | TA15 | HTR1E | OR2I2 |
| GPR52 | CCRL2 | GPR8 | TG1019 | PGR24 | SLT |
| OR51Q1 | GPR78 | OPN1LW | HTR5B | HM74A | MRGA2 |
| MRGA3 | MRGA4 | MRGA5 | MRGA6 | MRGA7 | MRGA8 |
| MRGB1 | MRGB2 | MRGB3 | MRGB4 | OR51E1 | MRGB5 |
| OR51E2 | CMKBR1L1 | FPR-RS1 | FPR-RS3 | FPR-RS4 | TA8 |
| PGR15L | OR2A1 | OR2A7 | P2RY11 | TA7 | OR7D2 |
| P2Y3L | TCP10C | OR7E102 | GPR103L | GNRHR2 | PGR9 |
| EMR2 | EMR3 | OR8B3 | OR4N4 | PGR6 | |
| MGRX1 | MGRX2 | MGRX3 | MGRX4 | | |

Other tissues

GPCRs listed in Table 1 may also be expressed in the pancreas, bone and joints, breasts, immune system, or systemically. These GPCRs may thus be involved in metabolic

diseases or disorders and diseases or disorders of the pancreas, bone and joints, breast, or immune system. Any GPCRs involved in these diseases are targets for diagnostic tests, drug design, and therapy.

Exemplary diseases and disorders of the pancreas include ACTHoma, acute

5 pancreatitis, adult onset diabetes, annulare pancreas, carcinoid syndrome, carcinoid tumors, carcinoma of the pancreas, chronic pancreatitis, congenital cysts, Cushing's syndrome, cystadenocarcinoma, cystic fibrosis (mucoviscidosis, fibrocystic disease), diabetes mellitus, ectopic pancreatic tissue, gasterinoma, gastrin excess, glucagon excess, glucagonomas, GRFomas, hereditary pancreatitis, hyperinsulinism, impaired insulin release, infected

10 pancreatic necrosis, insulin resistance, insulinomas, islet cell hyperplasia, islet cell neoplasms, juvenile onset diabetes, macroamylasemia, maldevelopment of the pancreas, maturity-onset diabetes of the young, metastatic neoplasms, mucinous cystadenoma, neoplastic cysts, nonfunctional pancreatic endocrine tumors, pancreas divisum, pancreatic abcess, pancreatic cancer, pancreatic cholera, pancreatic cysts, pancreatic endocrine tumor

15 causing carcinoid syndrome, pancreatic endocrine tumor causing hypercalcemia, pancreatic endocrine tumors, pancreatic exocrine insufficiency, pancreatic pleural effusion, pancreatic polypeptide excess, pancreatic pseudocyst, pancreatic trauma, pancreatogenous ascites, serous cystadenoma, Shwachman's syndrome, somatostatin excess, somatostatinoma syndrome, traumatic pancreatitis, type 1 (insulin-dependent) diabetes, type 2 (non-insulin-

20 dependent) diabetes, vasoactive intestinal polypeptide excess, VIPomas, and Zollinger-Ellison syndrome.

Exemplary diseases and disorders of the bone and joints include achondroplasia, acute bacterial arthritis, acute pyogenic osteomyelitis, Albright's syndrome, alkaptonuria (ochronosis), aneurysmal bone cyst, ankylosing spondylitis, arthritic, arthropathies

25 associated with hemoglobinopathies, arthropathy of acromegaly, arthropathy of hemochromatosis, bone cysts, calcium hydroxyapatite deposition disease, calcium pyrophosphate deposition disease, chondrocalcinosis, chondroma, chondrosarcoma, chondrochondritis, chondromblastoma, congenital dislocation of the hip, congenital disorders of joints, echondromatosis (dyschondroplasia, Ollier's disease), erosive

30 osteoarthritis, Ewing's sarcoma, Felty's syndrome, fibromyalgia, fibrous cortical defect,

fibrous dysplasia (McCune-Albright syndrome, fungal arthritis, ganglion, giant cell tumor, gout, hematogenous osteomyelitis, hemophilic arthropathy, hereditary hyperphosphatasia, hyperostosis, hyperostosis frontalis interna, hyperparathyroidism (osteitis fibrosa cystica), hypertrophic osteoarthropathy, infections diseases of joints, juvenile rheumatoid arthritis
 5 (Still's disease), Lyme disease, lymphoid neoplasms, melorheostosis, metabolic diseases of joints, metastatic carcinoma, metastatic neoplasms, monostatic fibrous dysplasia, multiple exostoses (diaphyseal aclasis, osteochondromatosis), neoplasms, neuropathic joint (Charcot's joint), osteoarthritis, osteoarthrosis, osteoblastoma, osteochondroma (exostosis), osteogenesis imperfecta (brittle bone disease), osteoid osteoma, osteoma, osteomalacia,
 10 osteomyelitis, osteomyelosclerosis, osteopetrosis (marble bone disease, Albers-Schönberg disease), osteopoikilosis, osteoporosis (osteopenia), osteosarcoma, osteosclerosis, Paget's disease of bone (osteitis deformans), parasitic arthritis, parosteal osteosarcoma, pigmented villonodular synovitis, polyostotic fibrous dysplasia, postinfectious or reactive arthritis, progressive diaphyseal dysplasia (Camurati-Engelmann disease), pseudogout, psoriatic
 15 arthritis, pyknodysostosis, pyogenic arthritis, reflex sympathetic dystrophy syndrome, relapsing polychondritis, rheumatoid arthritis, rickets, senile osteoporosis, sickle cell disease, spondyloepiphyseal dysplasia, synovial chondromatosis, synovial sarcoma, syphilitic arthritis, talipes calcaneovalgus, talipes equinovarus, thalassemia, Tietze's syndrome, tuberculosis of bone, tuberculous arthritis, unicameral bone cyst (solitary bone
 20 cyst), and viral arthritis.

Exemplary diseases and disorders of the immune system include abnormal neutrophil function, acquired immunodeficiency, acute rejection, Addison's disease, advanced cancer, aging, allergic rhinitis, angioedema, arthrus-type hypersensitivity reaction, ataxia-telangiectasia, autoimmune disorders, autoimmune gastritis, autosomal recessive
 25 agammaglobulinemia, blood transfusion reactions, Bloom's syndrome, Bruton's congenital agammaglobulinemia, bullous pemphigoid, Chédiak-Higashi syndrome, chronic active hepatitis, chronic granulomatous disease of childhood, chronic rejection, chronic renal failure, common variable immunodeficiency, complement deficiency, congenital (primary) immunodeficiency, contact dermatitis, deficiencies of immune response, deficiency of the
 30 vascular response, dermatomyositis, diabetes mellitus, disorders of microbial killing,

- disorders of phagocytosis, Goodpasture's syndrome, graft rejection, graft-versus-host disease, granulocyt deficiency, granulocytic leukemia, Graves' disease, Hashimoto's thyroiditis, hemolytic anemia, hemolytic disease of the newborn, HIV infection (AIDS), Hodgkin's disease, hyperacute rejection, hyper-IgE syndrome, hypersensitivity
- 5 pneumonitis, hypoparathyroidism, IgA deficiency, IgG subclass deficiencies, immunodeficiency with thymoma, immunoglobulin deficiency syndromes, immunologic hypersensitivity, immunosuppressive drug therapy, infertility, insulin-resistant diabetes mellitus, interferon γ receptor deficiency, interleukin 12 receptor deficiency, iron deficiency, juvenile insulin-dependent diabetes mellitus, Kaposi's sarcoma, lazy leuknock
- 10 outcyte syndrom, localized type 1 hypersensitivity, lymphocytic leukemia, lymphoma, malignant B cell lymphoma, major histocompatibility complex class 2 deficiency, mixed connective tissue disease, multiple myeloma, myasthenia gravis, myeloperoxidase deficiency, neutropenia, nude syndrome, pemphigus vulgaris, pernicious anemia, postinfectious immunodeficiency, primary biliary cirrhosis, primary immunodeficiency,
- 15 primary T cell immunodeficiency, progressive systemic sclerosis, protein-calorie malnutrition, purine nucleoside phosphorylation deficiency, rheumatic fever, rheumatoid arthritis, secondary immunodeficiency, selective (isolated) IgA deficiency, serum sickness type hypersensitivity reaction, severe combined immunodeficiency, Sjögren's syndrome, sympathetic ophthalmitis, systemic lupus erythematosus, systemic mastocytosis, systemic
- 20 type 1 hypersensitivity, T cell receptro deficiency, T lymphopenia (Nezelof's syndrome), thrombocytopenia, thymic hypoplasia (DiGeorge syndrome), thymic neoplasms, thymoma (Goode's syndrome), transient hypogammaglobulinemia of infancy, type 1 (immediate) hypersensitivity (atopy, anaphylaxis), type 2 hypersensitivity, type 3 hypersensitivity (immune complex injury), type 4 (delayed) hypersensitivity, urticaria, variable
- 25 immunodeficiency, vitiligo, Wisknock outtt-Aldrich syndrom, x-linked agammaglobulinemia, x-linked immunodeficiency with hyper IgM, x-linked lymphoproliferative syndrome, and zap70 tyrosine kinase deficiency.

- Exemplary diseases and disorders of the breasts include acute mastitis, breast abcess, carcinoma, chronic mastitis, congenital breast anomalies, cystic mastopathy, ductal
- 30 carcinoma, ductal carcinoma in situ, ductal papilloma, fat necrosis, fibroadenoma,

fibrocystic changes, fibrocystic disease, galactorrhea, granular cell tumor, gynecomastia, infiltrating ductal carcinoma, inflammatory breast carcinoma, inflammatory breast lesions, invasive lobular carcinoma, juvenile hypertrophy of the breast, lactating adenoma, lobular carcinoma in situ, neoplasms, Paget's disease of the nipple, phyllodes tumor (cystosarcome
 5 phyllodes), polymastia, polymazia, polythelia, silicone granuloma, supernumerary breast, and supernumerary nipples.

Exemplary metabolic or nutritive diseases or disorders include 5,10-methylenetetrahydrofolate reductase deficiency, achondrogenesis type 1B, acid α -1,4 glucosidase deficiency, acquired generalized lipodystrophy (Lawrence syndrome), acuiored
 10 partial lipodystrophy (Barraquer-Simons syndrome), acute intermittent porphyria, acute panniculitis, adenine phosphoribosyltransferase deficiency, adenosine deaminase deficiency, adenylosuccinate lyase deficiency, adiposis dolorosa (Dercum disease), ALA dehydratase-deficient porphyria, albinism, alkaptonuria, amulopectinosis, Andersen disease, argininemia, argininosuccinic aciduria, astelosteogenesis type 2, Bartter's syndrome, benign
 15 familial neonatal epilepsy, benign fructosuria, benign recurrent and progressive familial intrahepatic cholestasis, biotin deficiency, branching enzyme deficiency, calcium deficiency, carnitine transport defect, choline deficiency, choline toxicity, chromium deficiency, chronic fat malabsorption, citrullinemia, classic branched-chain ketoaciduria, classic cystinuria, congenital chloridorrhea, congenital erythropoietic porphyria, congenital
 20 generalized lipodystrophy, congenital myotonia, copper deficiency, copper toxicity, cystathionine β -synthase deficiency, cystathioninuria, cystic fibrosis, cystinosis, cystinuria, Darier disease, defect in transport of long-chain fatty acids, deficiency of cobalamin coenzyme deficiency, Dent's syndrome, diatrophic dysplasia, dibasic aminoaciduria, dicarboxylic aminoaciduria, dihydropyrimidine dehydrogenase deficiency, distal renal
 25 tubular acidosis, dry beriberi, Dubin-Johnson syndrome, dysbetalipoproteinemia, end-organ insensitivity to vitamin D, erythropoietic protoporphyria, Fabry disease, failure of intestinal absorption, familial apoprotein C2 deficiency, familial combined hyperlipidemia, familial defective Apo B100, familial goiter, familial hypercholesterolemia, familial
 30 hypertriglyceridemia, familial hypophosphatemic rickets, familial lipoprotein lipase deficiency, familial partial lipodystrophy, Fanconi-Bickel syndrome, fluoride deficiency,

- folate malabsorption, folic acid deficiency, formiminoglutamic aciduria, fructose 1,6 diphosphatase deficiency, galactokinase deficiency, galactose 1-phosphate uridylyl transferase deficiency galactosemia, Gaucher disease, Gitelman's syndrome, globoid cell leukodystrophy, glucose-6-phosphatase deficiency, glucose-6-phosphatase deficiency, glucose-6-phosphate translocase deficiency,
- 5 glucose-galactose malabsorption, glucose-transporter protein syndrome, glutaric aciduria, glycogen storage disease type 2, glycogen storage disease type Ib, glycogen storage disease type ID, glycogen synthase deficiency, gout, Hartnup disease, hawkinsinuria, hemochromatosis, hepatic glycogenosis with renal fanconi syndrome, hepatic lipase deficiency, hepatic porphyria, hereditary coproporphyria, hereditary fructose intolerance,
- 10 hereditary xanthinuria, Hers disease, histidinemia, histidinuria, HIV-1 protease inhibitor-induced lipodystrophy, homocitrullinuria, homocystinuria, homocystinuria, homocystinuria and methylmalonic acidemia, homocystinurias, Hunter syndrome, Hurler disease, Hurler-Scheie disease, hypophosphatemic rickets, hyperammonemia, hyperammonemia, hypercholesterolemia, hypercystinuria, hyperglycinemia, hyperhydroxyprolinemia,
- 15 hyperkalemic periodic paralysis, hyperleucineisoleucinemia, hyperlipoproteinemias, hyperlysinemia, hypermagnesemia, hypermetabolism, hypermethioninemia, hyperornithinemia, hyperoxaluria, hyperphenylalaninemia with primapterinuria, hyperphenylalaninemias, hyperphosphatemia, hyperprolinemia, hypertriglyceridemia, hyperuricemia, hypervitaminosis A, hypervitaminosis D,
- 20 hypocholesterolemia, hypometabolism, hypophosphatemia, hypouricemia, hypovitaminosis A, hypoxanthine phosphoribosyltransferase deficiency, iminoglycinuria, iminopeptiduria, intermittent branched-chain ketoaciduria, intestinal malabsorption, iodine deficiency, iron deficiency, isovaleric acidemia, Jervell and Lange-Nielsen syndrome, juvenile pernicious anemia, keshan disease, Knock out/saknock out/ff's syndrome, kwashiorknock out,
- 25 leukodystrophies, Liddle's syndrome, lipodystrophies, lipomatosis, liver glycogenoses, liver phosphorylase kinase deficiency, long QT syndrome, lysinuria, lysosomal storage diseases, magnesium deficiency, malabsorptive diseases, malignant hyperphenylalaninemia, manganese deficiency, marasmus, Maroteaux-Lamy disease, McArdle disease, Menkes' disease, metachromatic leukodystrophy, methionine
- 30 malabsorption, methylmalonic acidemia, molybdenum deficiency, monosodiumurate gout,

Morquio syndrome, mucopolysaccharidoses, multiple carboxylase
 deficiency syndrome, multiple symmetric lipomatosis, Madelung disease, muscle
 glycogenoses, muscle phosphofructokinase deficiency, muscle phosphorylase deficiency,
 myoadenylate deaminase deficiency, nephrogenic diabetes insipidus, nesidioblastosis of
 5 pancreas, niacin deficiency, niacin toxicity, Niemann-Pick disease, obesity, orotic aciduria,
 osteomalacia, paramyotonia congenita, pellagra, Pendred syndrome, phenylketonuria,
 phenylketonuria type 1, phenylketonuria type 2, phenylketonuria type 3, phosphate
 deficiency, phosphoribosylpyrophosphate synthetase overactivity, polygenic
 hypercholesterolemia, Pompe disease, porphyria cutanea tarda, porphyrias, primary bile
 10 acid malabsorption, primary hyperoxaluria, primary hypoalphalipoproteinemia, propionic
 acidemia, protein-energy malnutrition, proximal renal tubular acidosis, purine nucleoside
 phosphorylase deficiency, pyridoxine deficiency, pyrimidine 5'-nucleotidase deficiency,
 renal glycosuria, riboflavin deficiency, rickets, Rogers' syndrome, saccharopinuria,
 Sandhoff disease, Sanfilippo syndromes, sarcosinemia, Scheie disease, scurvy (vitamin C
 15 deficiency), selenium deficiency, selenosis, sialic acid storage disease, S-sulfo-L-cysteine,
 sulfite, thiosulfaturia, Tarui disease, Tay-Sachs disease, thiamine deficiency, tryptophan
 malabsorption, tryptophanuria, type 1 pseudohypoaldosteronism, type 3 glycogen storage
 disease (debrancher deficiency, limit dextrinosis), tyrosinemia, tyrosinemia type 1,
 tyrosinemia type 2, tyrosinemia type 3, uridine diphosphate galactose 4-epimerase
 20 deficiency, urocanic aciduria, variegate porphyria, vitamin B12 deficiency, vitamin C
 toxicity, vitamin D deficiency, vitamin D-resistant rickets, vitamin d-sensitive rickets,
 vitamin E deficiency, vitamin E toxicity, vitamin K deficiency, vitamin K toxicity, von
 Gierke disease, Wernicke's encephalopathy, wet beriberi, Wilson's disease, xanthurenic
 aciduria, X-linked sideroblastic anemia, zinc deficiency, zinc toxicity, α -ketoacidic aciduria,
 25 α -methylacetoacetic aciduria, β -hydroxy- β -methylglutaric aciduria, and β -methylcrotonyl
 glycinuria.

Combinatorial Expression of GPCRs

To begin a dissection of the functions of individual GPCRs, we analyzed the
 30 expression patterns of GPCRs in different mouse tissues. In these experiments, we used

RT-PCR with receptor-specific primers to analyze the expression of GPCR genes in RNAs from 17 peripheral tissues and 9 distinct regions of the brain (Figs. 3 and 4). The conditions used could consistently detect 50 or fewer RNA molecules per sample and could reliably reproduce the expression profiles of a number of known tissue-specific genes. All tissue samples were normalized according to their 18S rRNA content and were used at two concentrations (2ng and 20ng) of RNA to permit semi-quantitative evaluation.

Specific patterns of expression were clearly delineated. For example, GPR26 and TACR3 were exclusively expressed in the brain, while GPR91 and PGR16 were expressed solely in peripheral tissues. Four other genes, GPR73, EDG6, PGR15 and PGR21, were expressed in both brain and peripheral tissues. Also shown is GPRC5D, the only GPCR found to be expressed in just a single tissue, skin.

The results of RT-PCR analysis with 100 different GPCRs and 26 mouse tissues (17 peripheral tissues and 9 brain regions) are shown in Fig. 4. The data is presented as a semi-quantitative scattergram. The most remarkable finding was that 94% of GPCRs were detected in the brain, generally in 4 to 5 distinct anatomical areas. The largest number of genes was detected in the hypothalamus (82 genes), a brain region of high structural complexity. Individual peripheral tissues also showed expression of multiple different GPCRs, ranging from 12 genes in muscle to 69 genes in ovary.

Though individual GPCR genes were generally expressed in numerous tissues, most genes had unique expression profiles. Three groups with broadly related profiles were observed. In the first group were genes expressed primarily in peripheral tissues. Six of these genes were expressed exclusively in the peripheral tissues and not in the brain. The second group contained genes expressed primarily in brain. Of these 41 genes, 14 were solely expressed in brain and not in peripheral tissues. In the third group the genes were broadly expressed in the brain and throughout the periphery.

To further investigate GPCR expression in the brain, we used *in situ* hybridization to localize GPCR mRNA in brain sections. In these experiments 33P-labeled cRNA probes prepared from the coding regions of the receptor genes were hybridized to a series of sections throughout the entire brain, except the olfactory bulb.

Fig. 5 presents different expression patterns for GPCRs in the brain that are illustrative, but not totally inclusive, of those observed. One pattern is exemplified by PGR15, which was highly expressed in numerous subregions of the hypothalamus, with much less specific labeling noted in the adjacent thalamus or striatum (Fig. 5H). Other GPCRs, such as PGR7, were highly expressed in a single nucleus or region, with relatively little signal observed elsewhere (Fig. 5B). In contrast, several orphan receptors were widely distributed throughout the brain, but with highest levels noted in specific regions. For example, GPR63 was robustly expressed both in the pyramidal cells of the hippocampus (Fig. 5A) and in the Purkinje cell layer of the cerebellum (Fig. 5D). Other orphan receptors exhibited a non-localized profile. For instance, GRCA was distributed in nearly every neuronal region in the entire brain, while the white matter regions containing processes were conspicuously devoid of GRCA mRNA (Fig. 5C). In contrast, the orphan gene GPR37 was diffusely expressed in scattered cells from the frontal cortex (Fig. 5E) to the medulla, in both white and gray matter, suggesting a glial cell distribution. A number of GPCRs were prominently expressed in circumventricular organs, the choroid plexus, and the ependymal cells of the ventricles, areas involved in chemical communication between the brain and periphery. This pattern is exemplified by GPR50, found at very high levels in virtually all cells lining the ventral portion of the third ventricle (Fig. 5G).

The *in situ* hybridization analyses demonstrate that the expression of GPCRs in the brain is even more diverse than could be revealed by RT-PCR profiling. In addition to confirming the results obtained by RT-PCR for different brain regions, these studies reveal that GPCRs are expressed in diverse patterns within those regions, further highlighting the involvement of combinations of GPCRs in different functions.

25 **Therapeutic Compounds**

A large number of GPCRs are found in the brain. Excluding the large family of odor receptors, over 89% of known GPCRs are active in the brain. Of particular importance is that up to 81% of the known GPCRs in the brain are active in the HAP. We hypothesize that the majority of these receptors serve as modulators of behavior, memory, cognition, pain, and instinctive functions. In animal models, defects in brain GPCRs have been found

to lead to various disorders, including increased aggression, hyperactivity, learning deficits, and altered pain perception.

GPCRs, especially those in the nervous system, are ideal targets for drug development. Most GPCRs are located in the plasma membranes of cells, where they can
5 be easily accessed by pharmaceutical compounds. There are significant numbers and varieties of GPCRs to provide for a high degree of specificity, a key requirement in the discovery of medicines with few or limited side effects. Given these properties, GPCRs, as a group, have emerged among the most coveted targets for drug development.

The preference for GPCRs as specific drug targets derives, not only from their
10 central role in biological processes, but also from the discriminating ability that these molecules have in recognizing and responding to their signals. Many GPCRs exist in several similar, but subtly distinct subtypes, which are found in different cells in the body. Such variety of sequence and location provides a high degree of selectivity, allowing the discovery of drugs which specifically affect one subtype of receptor, but not another. This
15 selectivity substantially reduces the risk of unwanted side effects. In addition, techniques of medicinal chemistry known in the art can impact the localization of drugs to different compartments within the body. These techniques also contribute to the specificity of drugs.

In the case of the histamine GPCRs, for instance, subtypes are distributed in the central nervous, cardiopulmonary, and gastrointestinal systems. Yet, each subtype of the
20 histamine receptor is a target of a different medicine. Drugs selective for histamine GPCRs subtypes include Tagamet®, Zantac®, Seldane®, and Dramamine®. Each of these drugs is subtly different from the others, and each has a different target site and therapeutic effect.

GPCR polypeptides of the present invention have one or more biological functions that may be of relevance in one or more behavioral disorders, in particular the disorders of
25 the invention herein before mentioned. As the GPCR polypeptides may be expressed in other organs and tissues of the body, they may be of relevance to diseases and disorders that involve those organs and tissues. It is therefore useful to identify compounds that modulate GPCR biological activity, expression level, or stability. Accordingly, in a further aspect, the present invention provides methods of screening candidate compounds to identify those
30 that modulate GPCR biological activity, expression level, or stability. Such methods

identify potential modulators that may be employed for therapeutic and prophylactic purposes for treating various disorders, e.g., behavioral disorders as described herein. Compounds may be identified from a variety of sources, for example, cells, cell-free preparations, chemical libraries, collections of chemical compounds, and natural product
5 mixtures. Modulators so identified may be natural or modified ligands, or small molecules. Such small molecules preferably have a molecular weight below 2,000 daltons, more preferably between 300 and 1,000 daltons, and most preferably between 400 and 700 daltons. It is preferred that these small molecules be organic molecules.

The screening method may simply measure the interaction of a candidate compound
10 to the polypeptide, or to cells or membranes bearing the polypeptide, or a fusion protein thereof, by means of a label directly or indirectly associated with the candidate compound, or, alternatively, the polypeptide. Alternatively, the screening method may involve measuring or detecting (qualitatively or quantitatively) the competitive interaction of a candidate compound to the polypeptide against a labeled substrate. Further, these screening
15 methods may test whether the candidate compound activates or inhibits the GPCR polypeptide, using detection systems appropriate to the cells bearing the polypeptide. Further, the screening methods may include the steps of mixing a candidate compound with a solution containing a GPCR polypeptide of the present invention, to form a mixture, measuring GPCR biological activity in the mixture, and comparing the GPCR activity of the
20 mixture to a control mixture that contains no candidate compound.

Polypeptides of the present invention may be employed in conventional low capacity screening methods and also in high-throughput screening (HTS) formats. Such HTS formats include not only the well-established use of 96- and, more recently, 384-well and 1536-well micotiter plates, but also emerging methods such as the nanowell method described by
25 Schullek et al., *Anal Biochem.*, 246, 20-29, (1997).

Fusion proteins and tagged recombinant proteins, such as those made from the F_c portion of an antibody and a GPCR polypeptide or epitope tagged GPCR, can also be used for high-throughput screening (HTS) assays to identify modulators of the GPCR polypeptides of the present invention (see, e.g., Bennett et al., *J. Mol. Recognit.*, 8:52-58,
30 1995; and Johanson et al., *J. Biol. Chem.*, 270:9459-9471, 1995).

Drug Screening

A GPCR of the invention and its gene or cDNA can be used in screening assays for identification of compounds that modulate its activity and which may therefore be potential
5 drugs. Useful proteins include wild-type and polymorphic GPCRs or fragments thereof (e.g., an extracellular domain, an intracellular domain, or a transmembrane domain), in a recombinant form or endogenously expressed. Drug screens to identify compounds acting on a normally occurring or an exogenously expressed GPCR may employ any functional feature of the protein. In one example, the phosphorylation state or other post-translational
10 modification is monitored as a measure of GPCR biological activity. In addition, drug screening assays may be based upon the ability of the protein to transduce a signal across a membrane or upon the ability to activate a G protein or another molecule. For example, the ability of a G protein to bind GTP may be assayed. Alternatively, a target of the G protein can be used as a measure of GPCR biological activity.

15 Drug screening assays can also be based upon the ability of a GPCR to interact with other proteins. Such interacting proteins can be identified by a variety of methods known in the art, including, for example, radioimmunoprecipitation, co-immunoprecipitation, co-purification, and yeast two-hybrid screening. Such interactions can be further assayed by means including but not limited to fluorescence polarization or scintillation proximity
20 methods. Drug screens can also be based upon putative functions of a GPCR polypeptide deduced from structure determination (e.g., by x-ray crystallography) of the protein and comparison of its 3-D structure to that of proteins with known functions. Molecular modeling of compounds that bind to the protein using a 3-D structure may also be used to determine drug candidates. Drug screens can be based upon a function or feature apparent
25 upon creation of a transgenic or knock-out mouse, or upon overexpression of the protein or protein fragment in mammalian cells *in vitro*. Moreover, expression of a mammalian (e.g., human) GPCR in yeast or *C. elegans* allows for screening of candidate compounds in wild-type and polymorphic backgrounds, as well as screens for polymorphisms that enhance or suppress a GPCR-dependent phenotype. Modifier screens can also be performed in a
30 GPCR transgenic or knock-out mouse.

Additionally, drug screening assays can be based upon GPCR functions deduced upon antisense nucleic acid inhibition or RNA interference (RNAi) with the GPCR's gene function. Intracellular localization of a GPCR, or effects which occur upon a change in intracellular localization of the protein, can also be used as an assay for drug screening.

- 5 Immunocytochemical methods can be used to determine the exact location of a GPCR protein.

- Human and rodent GPCRs or peptides derived from GPCRs can be used as antigens to raise antibodies, including monoclonal antibodies. Such antibodies will be useful for a wide variety of purposes, including but not limited to functional studies and the
- 10 development of drug screening assays and diagnostics. Monitoring the influence of agents (e.g., drugs, compounds) on the expression or biological activity of a GPCR can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase gene expression, protein levels, or biological activity of a GPCR can be monitored in clinical trials of
- 15 subjects exhibiting altered gene expression, protein levels, or biological activity of that GPCR. Alternatively, the effectiveness of an agent determined by a screening assay to modulate the gene expression, protein levels, or biological activity of a GPCR can be monitored in clinical trials of subjects exhibiting decreased altered gene expression, protein levels, or biological activity. In such clinical trials, the expression or activity of a GPCR
- 20 and, preferably, other genes that have been implicated in one or more diseases or disorders can be used to ascertain the effectiveness of a particular drug.

- For example, and not by way of limitation, genes that are modulated in cells by treatment with an agent (e.g., compound, drug, or small molecule) that modulates the biological activity of a GPCR polypeptide (e.g., identified in a screening assay as described
- 25 herein) can be identified. Thus, to study the effect of agents on one or more diseases or disorders in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of a GPCR and other genes implicated in the disorder. The levels of gene expression can be quantified by northern blot analysis or RT-PCR, followed by real time PCR, or, alternatively, by measuring the amount of protein produced, by one of a
- 30 number of methods known in the art, or by measuring the levels of biological activity of a

GPCR or other genes. In this way, the expression of a GPCR polypeptide can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during, treatment of the individual with the agent. For in vivo studies MRI, pet scans etc may be better assays.

5 In one embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting
10 the level of expression of a GPCR polypeptide, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of a GPCR polypeptide, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of a GPCR polypeptide, mRNA, or genomic DNA in the pre-administration sample
15 with the polypeptide, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of a GPCR polypeptide to higher levels than detected, i.e., to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be
20 desirable to decrease expression or activity of a GPCR polypeptide to lower levels than detected.

 A GPCR polynucleotide can be used as a tool to express the GPCR polypeptide in an appropriate cell *in vitro* or *in vivo* (gene therapy), or can be cloned into expression vectors that can be used to produce large enough amounts of a GPCR polypeptide for use in
25 *in vitro* assays for drug screening. Expression systems that may be employed include baculovirus, herpes virus, adenovirus, adeno-associated virus, bacterial systems, and eukaryotic systems such as CHO cells. Naked DNA and DNA-liposome complexes can also be used.

 Assays of GPCR activity include binding to intracellular interacting proteins.
30 Furthermore, assays may be based upon the molecular dynamics of macromolecules,

metabolites, and ions by means of fluorescent-protein biosensors. Alternatively, the effect of candidate modulators on expression or activity may be measured at the level of GPCR production using the same general approach in combination with standard immunological detection techniques, such as western blotting or immunoprecipitation with a GPCR polypeptide-specific antibody. Again, useful modulators are identified as those that produce a change in GPCR polypeptide production. Modulators may also affect GPCR activity without any effect on expression level.

Candidate modulators may be purified (or substantially purified) molecules or may be one component of a mixture of compounds (e.g., an extract or supernatant obtained from cells). In a mixed compound assay, GPCR expression is tested against progressively smaller subsets of the candidate compound pool (e.g., produced by standard purification techniques, e.g., HPLC or FPLC) until a single compound or minimal compound mixture is demonstrated to modulate GPCR expression. Alternatively, diverse mixtures (i.e., libraries) of test compounds may be assayed in such a way that the pattern of response indicates which compounds in the various mixtures are responsible for the effect (deconvolution).

Agonists, antagonists, or mimetics found to be effective at modulating the level of cellular GPCR expression or activity may be confirmed as useful in animal models (for example, mice, pigs, dogs, or chickens). For example, the compound may increase survival or mitigate distress in animal models of one or more diseases or disorders.

A gene encoding a GPCR polypeptide may have a polymorphism that may be, for example, a causative or risk factor of the diseases and disorders discussed below. Screening methods that identify polymorphisms may be of diagnostic and therapeutic benefit. For example, early detection of a particular polymorphism may enable preventative treatment or prediction of a patient's response (e.g., increased or decreased efficacy or undesirable side effects of treatment). Methods of identifying polymorphisms include PCR, RT-PCR, northern blot (e.g., using clones encompassing discrete regions of cDNA), Southern blot, polymorphic specific probes, sequencing analysis, hybridization assays, restriction endonuclease analysis, and exon-specific amplification.

One method for altering the biological activity of a GPCR polypeptide is to increase or decrease the stabilization of the protein or to prevent its degradation. Thus, it would be

useful to identify polymorphisms in a GPCR polypeptide that lead to altered protein stability. These polymorphisms can be incorporated into any protein therapy or gene therapy undertaken for the treatment of any condition resulting from loss of GPCR biological activity. Similarly, compounds that increase the stability of a wild-type GPCR polypeptide or decrease its catabolism may also be useful for the treatment of any condition resulting from loss of GPCR biological activity. Such polymorphisms and compounds can be identified using the methods described herein. In an analogous manner, decreasing stability may be used to decrease the activity of a GPCR.

In one example, cells expressing a GPCR polypeptide having a polymorphism are transiently metabolically labeled during translation and the half-life of the GPCR polypeptide is determined using standard techniques. Polymorphisms that increase the half-life of a GPCR polypeptide are ones that increase GPCR protein stability. These polymorphisms can then be assessed for biological activity. They can also be used to identify proteins that affect the stability of GPCR mRNA or protein. One can then assay for compounds that act on these factors or on the ability of these factors to bind a GPCR.

In another example, cells expressing a wild-type GPCR polypeptide are transiently metabolically labeled during translation, contacted with a candidate compound, and the half-life of the GPCR polypeptide is determined using standard techniques. Compounds that modulate the half-life of a GPCR polypeptide are useful compounds in the present invention.

If desired, treatment with a modulator of a GPCR of the invention may be combined with any other therapy.

A GPCR polypeptide (purified or unpurified) can be used in an assay to determine its ability to bind another protein (including, but not limited to, proteins found to specifically interact with a GPCR). The effect of a compound on that binding is then determined.

Methods of identifying compounds having the foregoing properties can be identified by standard methods known in the art. Exemplary methods for identifying compounds are described herein.

Identification of Molecules that Modulate GPCR Biological Activity

The effect of candidate compounds on GPCR biological activity or cell survival may be measured at the level of translation by using the general approach described above with standard protein detection techniques, such as western blotting, sandwich or competitive
5 immunoassays (both enzyme and radioactive tracer based) or immunoprecipitation with a GPCR-specific antibody as well as with quantitative immunoassays of GPCR regulated molecules.

Compounds that modulate the level of a GPCR may be purified, or substantially purified, or may be one component of a mixture of compounds such as an extract or
10 supernatant obtained from cells (Ausubel et al., *supra*). In an assay of a mixture of compounds, GPCR expression is measured in cells administered progressively smaller subsets of the compound pool (e.g., produced by standard purification techniques such as HPLC or FPLC) until a single compound or minimal number of effective compounds is demonstrated to affect GPCR expression. Alternatively, diverse mixtures (i.e., libraries) of
15 test compounds may be assayed in such a way that the pattern of response indicates which compounds in the various mixtures are responsible for the effect (deconvolution).

Compounds may also be screened for their ability to modulate GPCR biological activity. In this approach, the degree of GPCR biological activity in the presence of a candidate compound is compared to the degree of activity in its absence, under equivalent
20 conditions. Again, the screen may begin with a pool of candidate compounds, from which one or more useful modulator compounds are isolated in a step-wise fashion. GPCR biological activity may be measured by any standard assay, for example, those described herein.

Another method for detecting compounds that modulate GPCR biological activity is
25 to screen for compounds that interact physically with a GPCR polypeptide. These compounds may be detected, for example, by adapting interaction trap expression systems known in the art. These systems detect protein interactions using a transcriptional activation assay and are generally described by Gyuris et al. (Cell 75:791-803, 1993) and Field et al., (Nature 340:245-246, 1989), and are commercially available. Alternatively, a
30 GPCR polypeptide, or a fragment thereof, can be labeled with a detectable label (e.g., direct

¹²⁵I labelling of tyrosines or ¹²⁵I Bolton-Hunter reagent; Bolton et al. Biochem. J. 133:529, 1973). Candidate compounds previously arrayed in the wells of a multi-well plate are incubated with the labeled GPCR polypeptide. Following washing, the wells with bound, labeled GPCR polypeptide are identified. Data obtained using different concentrations of GPCR polypeptides are used to calculate values for the number, affinity, and association of the GPCR polypeptide with the candidate compounds. If desirable, the candidate compounds can be labeled instead of the GPCR polypeptide. Similarly, the GPCR polypeptide may be immobilized, e.g., in wells of a multi-well plate or on a solid support, and soluble compounds are then contacted with the GPCR polypeptide. Upon removal of unbound compound, the identity of bound candidate compounds is ascertained. Compounds that bind are considered to be candidate modulators of GPCR biological activity. Alternatively, interaction of unlabeled GPCR may be detected using direct or indirect antibody labeling.

Another such method comprises the steps of (a) contacting a composition comprising a GPCR polypeptide with a compound suspected of binding GPCR; and (b) measuring binding between the compound and GPCR polypeptide. In one variation, the composition comprises a cell expressing a GPCR polypeptide on its surface. In another variation, an isolated GPCR polypeptide or cell membranes comprising the GPCR polypeptide are employed. The binding may be measured directly, e.g., by using a labeled compound, or may be measured indirectly by several techniques, including measuring intracellular signaling of the GPCR polypeptide induced by the compound (or measuring changes in the level of GPCR signaling). Following steps (a) and (b), compounds identified as binding a GPCR polypeptide can be further tested in other assays including, but not limited to, in vivo models, in order to confirm or quantitate binding to a GPCR polypeptide.

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches

are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. USA.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994) *J. Med. Chem.* 37:2678; 5 Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop et al. (1994) *J. Med. Chem.* 37:1233. Libraries of compounds may be presented in solution (e.g., Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), 10 chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP 409), plasmids (Cull et al. (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla et al. (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310).

15 Specific binding molecules, including natural ligands and synthetic compounds, can be identified or developed using isolated or recombinant GPCR products, GPCR variants, or preferably, cells expressing such products. Binding partners are useful for purifying GPCR products and detection or quantification of GPCR products in fluid and tissue samples using known immunological procedures. Binding molecules are also manifestly useful in 20 modulating (i.e., blocking, inhibiting or stimulating) biological activities of a GPCR polypeptide, especially those activities involved in signal transduction. The DNA and amino acid sequence information provided by the present invention also makes possible identification of binding partner compounds with which a GPCR polypeptide or polynucleotide will interact. Methods to identify binding partner compounds include 25 solution assays, in vitro assays wherein GPCR polypeptides are immobilized, and cell-based assays. Identification of binding partner compounds of GPCR polypeptides provides candidates for therapeutic or prophylactic intervention in pathologies associated with GPCR normal and aberrant biological activity.

The invention includes several assay systems for identifying GPCR polypeptide 30 binding partners. In solution assays, methods of the invention comprise the steps of (a)

contacting a GPCR polypeptide with one or more candidate binding partner compounds and
(b) identifying the compounds that bind to the GPCR polypeptide. Identification of the
compounds that bind the GPCR polypeptide can be achieved by isolating the GPCR
polypeptide/binding partner complex, and separating the binding partner compound from
5 the GPCR polypeptide.

An additional step of characterizing the physical, biological, and/or biochemical
properties of the binding partner compound is also comprehended in another embodiment of
the invention, wherein compounds identified as binding GPCR can be further tested in other
assays including, but not limited to, in vivo models, in order to confirm or quantitate
10 binding to GPCR. In one aspect, the GPCR polypeptide/binding partner complex is isolated
using an antibody immunospecific for either the GPCR polypeptide or the candidate binding
partner compound.

In still other embodiments, either the GPCR polypeptide or the candidate binding
partner compound comprises a label or tag that facilitates its isolation, and methods of the
15 invention to identify binding partner compounds include a step of isolating the GPCR
polypeptide/binding partner complex through interaction with the label or tag. An
exemplary tag of this type is a poly-histidine sequence, generally around six histidine
residues, that permits isolation of a compound so labeled using nickel chelation. Other
labels and tags, such as the FLAG tag (Eastman Kodak, Rochester, NY), well known and
20 routinely used in the art, are embraced by the invention.

In one variation of an in vitro assay, the invention provides a method comprising the
steps of (a) contacting an immobilized GPCR polypeptide with a candidate binding partner
compound and (b) detecting binding of the candidate compound to the GPCR polypeptide.
In an alternative embodiment, the candidate binding partner compound is immobilized and
25 binding of GPCR is detected. Immobilization is accomplished using any of the methods
well known in the art, including covalent bonding to a support, a bead, or a
chromatographic resin, as well as non-covalent, high affinity interactions such as antibody
binding, or use of streptavidin/biotin binding wherein the immobilized compound includes a
biotin moiety. Detection of binding can be accomplished (i) using a radioactive label on the
30 compound that is not immobilized, (ii) using of a fluorescent label on the non-immobilized

compound, (iii) using an antibody immunospecific, for the non-immobilized compound, (iv) using a label on the non-immobilized compound that excites a fluorescent support to which the immobilized compound is attached, as well as other techniques well known and routinely practiced in the art.

5 The invention also provides cell-based assays to identify binding partner compounds of a GPCR polypeptide. In one embodiment, the invention provides a method comprising the steps of contacting a GPCR polypeptide expressed on the surface of a cell with a candidate binding partner compound and detecting binding of the candidate binding partner compound to the GPCR polypeptide. In a preferred embodiment, the detection comprises
10 detecting a calcium flux or other physiological event in the cell caused by the binding of the molecule.

Another aspect of the present invention is directed to methods of identifying compounds that bind to either a GPCR polypeptide or nucleic acid molecules encoding a GPCR polypeptide, comprising contacting GPCR polypeptide, or a nucleic acid molecule
15 encoding the same, with a compound, and determining whether the compound binds the GPCR polypeptide or a nucleic acid molecule encoding the same. Binding can be determined by binding assays which are well known to the skilled artisan, including, but not limited to, gel-shift assays, Western blots, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking,
20 interaction trap/two-hybrid analysis, southwestern analysis, ELISA, and the like, which are described in, for example, Current Protocols in Molecular Biology, 1999, John Wiley & Sons, NY, which is incorporated herein by reference in its entirety. The compounds to be screened include (which may include compounds which are suspected to bind GPCR polypeptides, or a nucleic acid molecule encoding the same), but are not limited to,
25 extracellular, intracellular, biologic or chemical origin. The methods of the invention also embrace ligands, especially neuropeptides, that are attached to a label, such as a radiolabel (e.g., ¹²⁵I, ³⁵S, ³²P, ³³P, ³H), a fluorescence label, a chemiluminescent label, an enzymic label and an immunogenic label.

Modulators falling within the scope of the invention include, but are not limited to,
30 non-peptide molecules such as non-peptide mimetics, non-peptide allosteric effectors, and

peptides. The GPCR polypeptide or polynucleotide employed in such a test may either be free in solution, attached to a solid support, borne on a cell surface or located intracellularly or associated with a portion of a cell. One skilled in the art can, for example, measure the formation of complexes between the GPCR polypeptide and the compound being tested.

- 5 Alternatively, one skilled in the art can examine the diminution in complex formation between a GPCR polypeptide and its substrate caused by the compound being tested.

In another embodiment of the invention, high throughput screening for compounds having suitable binding affinity to a GPCR polypeptide is employed. Briefly, large numbers of different test compounds are synthesized on a solid substrate. The peptide test
10 compounds are contacted with a GPCR polypeptide and washed. Bound GPCR is then detected by methods well known in the art. Purified polypeptides of the invention can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the protein and immobilize it on the solid support.

- 15 Generally, an expressed GPCR polypeptide can be used for HTS binding assays in conjunction with its defined ligand, in this case the corresponding neuropeptide that activates it. The identified peptide is labeled with a suitable radioisotope, including, but not limited to, ¹²⁵I, ³H, ³⁵S or ³²P, by methods that are well known to those skilled in the art. Alternatively, the peptides may be labeled by well-known methods with a suitable
20 fluorescent derivative (Baindur et al., Drug Dev. Res., 1994, 33, 373-398; Rogers, Drug Discovery Today, 1997, 2, 156-160).

Radioactive ligand specifically bound to the receptor in membrane preparations made from the cell line expressing the recombinant protein can be detected in HTS assays in one of several standard ways, including filtration of the receptor-ligand complex to separate
25 bound ligand from unbound ligand (Williams, Med. Res. Rev., 1991, 11, 147-184; Sweetnam, et al., J Natural Products, 1993, 56, 441-455). Alternative methods include a scintillation proximity assay (SPA) or a FlashPlate format in which such separation is unnecessary (Nakayama, Cur. Opinion Drug Disc. Dev., 1998, 1, 85-91; Boss et al., J Biomolecular Screening, 1998, 3, 285-292). Binding of fluorescent ligands can be detected
30 in various ways, including fluorescence energy transfer (FRET), direct

spectrophotofluorometric analysis of bound ligand, or fluorescence polarization (Rogers, Drug Discovery Today, 1997, 2, 156-160; Hill, Cur. Opinion Drug Disc. Dev., 1998, 1, 92-97).

Other assays may be used to identify specific ligands of a GPCR receptor, including
5 assays that identify ligands of the target protein through measuring direct binding of test ligands to the target protein, as well as assays that identify ligands of target proteins through affinity ultrafiltration with ion spray mass spectroscopy/HPLC methods or other physical and analytical methods. Alternatively, such binding interactions are evaluated indirectly using the yeast two hybrid system described in Fields et al., Nature, 340:245-246 (1989),
10 and Fields et al., Trends in Genetics, 10:286-292 (1994), both of which are incorporated herein by reference in its entirety.

The two-hybrid system is a genetic assay for detecting interactions between two proteins or polypeptides. It can be used to identify proteins that bind to a known protein of interest, or to delineate domains or residues critical for an interaction. Variations on this
15 methodology have been developed to clone genes that encode DNA binding proteins, to identify peptides that bind to a protein, and to screen for drugs. The two-hybrid system exploits the ability of a pair of interacting proteins to bring a transcription activation domain into close proximity with a DNA binding domain that binds to an upstream activation sequence (UAS) of a reporter gene, and is generally performed in yeast. The assay requires
20 the construction of two hybrid genes encoding (1) a DNA-binding domain that is fused to a first protein and (2) an activation domain fused to a second protein. The DNA-binding domain targets the first hybrid protein to the UAS of the reporter gene; however, because most proteins lack an activation domain, this DNA-binding hybrid protein does not activate transcription of the reporter gene. The second hybrid protein, which contains the activation
25 domain, cannot by itself activate expression of the reporter gene because it does not bind the UAS. However, when both hybrid proteins are present, the noncovalent interaction of the first and second proteins tethers the activation domain to the UAS, activating transcription of the reporter gene. For example, when the first protein is a GPCR gene product, or fragment thereof, that is known to interact with another protein or nucleic acid, this assay
30 can be used to detect agents that interfere with the binding interaction. Expression of the

reporter gene is monitored as different test agents are added to the system. The presence of an inhibitory agent results in lack of a reporter signal.

The yeast two-hybrid assay can also be used to identify proteins that bind to the gene product. In an assay to identify proteins that bind to a GPCR receptor, or fragment thereof, a fusion polynucleotide encoding both a GPCR receptor (or fragment) and a UAS binding domain (i.e., a first protein) may be used. In addition, a large number of hybrid genes each encoding a different second protein fused to an activation domain are produced and screened in the assay. Typically, the second protein is encoded by one or more members of a total cDNA or genomic DNA fusion library, with each second protein-coding region being fused to the activation domain. This system is applicable to a wide variety of proteins, and it is not even necessary to know the identity or function of the second binding protein. The system is highly sensitive and can detect interactions not revealed by other methods; even transient interactions may trigger transcription to produce a stable mRNA that can be repeatedly translated to yield the reporter protein.

Other assays may be used to search for agents that bind to the target protein. One such screening method to identify direct binding of test ligands to a target protein relies on the principle that proteins generally exist as a mixture of folded and unfolded states, and continually alternate between the two states. When a test ligand binds to the folded form of a target protein (i.e., when the test ligand is a ligand of the target protein), the target protein molecule bound by the ligand remains in its folded state. Thus, the folded target protein is present to a greater extent in the presence of a test ligand which binds the target protein, than in the absence of a ligand. Binding of the ligand to the target protein can be determined by any method that distinguishes between the folded and unfolded states of the target protein. The function of the target protein need not be known in order for this assay to be performed. Virtually any agent can be assessed by this method as a test ligand, including, but not limited to, metals, polypeptides, proteins, lipids, polysaccharides, polynucleotides and small organic molecules.

Another method for identifying ligands of a target protein is described in Wieboldt et al., *Anal. Chem.*, 69:1683-1691 (1997), incorporated herein by reference in its entirety. This technique screens combinatorial libraries of 20-30 agents at a time in solution phase

for binding to the target protein. Agents that bind to the target protein are separated from other library components by simple membrane washing. The specifically selected molecules that are retained on the filter are subsequently liberated from the target protein and analyzed by HPLC and pneumatically assisted electrospray (ion spray) ionization mass spectroscopy.

- 5 This procedure selects library components with the greatest affinity for the target protein, and is particularly useful for small molecule libraries.

Determining whether a test compound binds to a GPCR polypeptide can also be accomplished by measuring the intrinsic fluorescence of the GPCR polypeptide and determining whether the intrinsic fluorescence is modulated in the presence of the test
10 compound. Preferably, the intrinsic fluorescence of GPCR polypeptide is measured as a function of the tryptophan residue(s) of the GPCR. Preferably, fluorescence of the GPCR polypeptide is measured and compared to the fluorescence intensity of the GPCR polypeptide in the presence of the test compound, wherein a decrease in fluorescence intensity indicates binding of the test compound to a GPCR. Preferred methodology is set
15 forth in "Principles of Fluorescence Spectroscopy" by Joseph R. Lakowicz, New York, Plenum Press, 1983 (ISBN 0306412853) and "Spectrophotometry And Spectrofluorometry" by C.L. Bashford and D.A. Harris Oxford, Washington DC, IRL Press, 1987, each of which is incorporated herein by reference in its entirety.

Other embodiments of the invention comprise using competitive screening assays in
20 which neutralizing antibodies capable of binding a polypeptide of the invention specifically compete with a test compound for binding to the polypeptide. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants with a GPCR polypeptide. Radiolabeled competitive binding studies are described in A. H. Lin et al. Antimicrobial Agents and Chemotherapy, 1997, vol. 41, no. 10.
25 pp. 2127-2131, the disclosure of which is incorporated herein by reference in its entirety.

Another aspect of the present invention relates to methods of identifying a compound that binds to or modulates a GPCR polypeptide. The methods comprise contacting a composition comprising a GPCR and Peptide A with a test compound, or a plurality of test compounds, and determining whether the test compound competes with
30 Peptide A for binding to the GPCR polypeptide.

A decrease in the amount of the complex between Peptide A, or a protein homologous thereto, and the GPCR polypeptide in the presence of a test compound or compounds confirms that the compound or compounds binds to the GPCR polypeptide. In some embodiments, the affinity or displacement of Peptide A is measured, wherein a low
5 affinity indicates that the test compound interacts with the GPCR polypeptide. In these methods, the composition that comprises a GPCR polypeptide and Peptide A can be cells. Compounds identified as binding to a GPCR polypeptide are also expected to modulate GPCR activity. Binding of a test compound to a GPCR polypeptide can be determined by any of the binding assays described above.

10 The invention also provides methods for identifying a modulator of binding between a GPCR polypeptide and a GPCR binding partner, comprising the steps of (a) contacting a GPCR binding partner and a composition comprising a GPCR polypeptide in the presence and in the absence of a putative modulator compound; (b) detecting binding between the binding partner and the GPCR polypeptide; and (c) identifying a putative modulator
15 compound or a modulator compound in view of decreased or increased binding between the binding partner and the GPCR polypeptide in the presence of the putative modulator, as compared to binding in the absence of the putative modulator.

Following steps (a) and (b), compounds identified as modulating binding between GPCR and a GPCR binding partner can be further tested in other assays including, but not
20 limited to, in vivo models, in order to confirm or quantitate modulation of binding to a GPCR polypeptide.

GPCR binding partners that stimulate GPCR activity are useful as agonists in disease states or conditions characterized by insufficient GPCR signaling (e.g., as a result of insufficient activity of a GPCR ligand). GPCR binding partners that block ligand- mediated
25 GPCR signaling are useful as GPCR antagonists to treat disease states or conditions characterized by excessive GPCR signaling. In addition, GPCR modulators in general, as well as GPCR polynucleotides and polypeptides, are useful in diagnostic assays for such diseases or conditions.

In another aspect, the invention provides methods for treating a disease or abnormal
30 condition by administering to a patient in need of such treatment a substance that modulates

the activity or expression of a polypeptide having sequences selected from the group consisting of sequences listed in Table 1.

Agents that modulate (i.e., increase, decrease, or block) GPCR activity or expression may be identified by incubating a putative modulator with a cell containing a GPCR polypeptide or polynucleotide and determining the effect of the putative modulator on GPCR activity or expression. The selectivity of a compound that modulates the activity of GPCR can be evaluated by comparing its effects on GPCR to its effect on other GPCR compounds.

Methods of the invention to identify modulators include variations on any of the methods described above to identify binding partner compounds, the variations including techniques wherein a binding partner compound has been identified and the binding assay is carried out in the presence and absence of a candidate modulator. A modulator is identified in those instances where binding between the GPCR polypeptide and the binding partner compound changes in the presence of the candidate modulator compared to binding in the absence of the candidate modulator compound. A modulator that increases binding between the GPCR polypeptide and the binding partner compound is described as an enhancer or activator, and a modulator that decreases binding between the GPCR polypeptide and the binding partner compound is described as an inhibitor. Following identification of modulators, such compounds can be further tested in other assays including, but not limited to, in vivo models, in order to confirm or quantitate their activity as modulators.

The invention also comprehends high-throughput screening (HTS) assays to identify compounds that interact with or inhibit biological activity (i.e., affect enzymatic activity, binding activity, etc.) of a GPCR polypeptide. HTS assays permit screening of large numbers of compounds in an efficient manner. Cell-based HTS systems are contemplated to investigate GPCR receptor-ligand interaction. HTS assays are designed to identify "hits" or "lead compounds" having the desired property, from which modifications can be designed to improve the desired property. Chemical modification of the "hit" or "lead compound" is often based on an identifiable structure/activity relationship between the "hit" and the GPCR polypeptide.

Another aspect of the present invention is directed to methods of identifying compounds which modulate (i.e., increase or decrease) activity of GPCR comprising contacting a GPCR polypeptide with a compound, and determining whether the compound modifies activity of the GPCR. The activity in the presence of the test compared is
5 measured to the activity in the absence of the test compound. Where the activity of the sample containing the test compound is higher than the activity in the sample lacking the test compound, the compound will have increased activity. Similarly, where the activity of the sample containing the test compound is lower than the activity in the sample lacking the test compound, the compound will have inhibited activity.

10 The present invention is particularly useful for screening compounds by using GPCR in any of a variety of drug screening techniques. The compounds to be screened include (which may include compounds which are suspected to modulate GPCR activity), but are not limited to, extracellular, intracellular, biologic or chemical origin. The GPCR polypeptide employed in such a test may be in any form, preferably, free in solution,
15 attached to a solid support, on a cell surface or located intracellularly. One skilled in the art can, for example, measure the formation of complexes between GPCR and the compound being tested. Alternatively, one skilled in the art can examine the diminution in complex formation between GPCR and its substrate caused by the compound being tested.

The activity of GPCR polypeptides of the invention can be determined by, for
20 example, examining the ability to bind or be activated by chemically synthesized peptide ligands. Alternatively, the activity of GPCR polypeptides can be assayed by examining their ability to bind calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and photons. Alternatively, the activity of the GPCR polypeptides can be determined by examining the activity of effector molecules including,
25 but not limited to, adenylate cyclase, phospholipases and ion channels. Thus, modulators of GPCR polypeptide activity may alter a GPCR receptor function, such as a binding property of a receptor or an activity such as G protein-mediated signal transduction or membrane localization. In various embodiments of the method, the assay may take the form of an ion flux assay, a yeast growth assay, a non-hydrolyzable GTP assay such as a [35S]-GTP γ S
30 assay, a cAMP assay, an inositol triphosphate assay, a diacylglycerol assay, an Aequorin

assay, a Luciferase assay, a FLIPR assay for intracellular Ca^{2+} concentration, a mitogenesis assay, a MAP Kinase activity assay, an arachidonic acid release assay (e.g., using $[3 \text{ H}]$ -arachidonic acid), and an assay for extracellular acidification rates, as well as other binding or function-based assays of GPCR activity that are generally known in the art. In several of these embodiments, the invention comprehends the inclusion of any of the G proteins known in the art, such as G 16, G 15, Gs, Gi, Gz, Gq or chimeric G proteins, and the like. GPCR activity can be determined by methodologies that are used to assay for FARP activity, which is well known to those skilled in the art. Biological activities of GPCR receptors according to the invention include, but are not limited to, the binding of a natural or an unnatural ligand, as well as any one of the functional activities of GPCRs known in the art. Non-limiting examples of GPCR activities include transmembrane signaling of various forms, which may involve G protein association and/or the exertion of an influence over G protein binding of various guanidylate nucleotides; another exemplary activity of GPCRs is the binding of accessory proteins or polypeptides that differ from known G proteins.

The modulators of the invention exhibit a variety of chemical structures, which can be generally grouped into non-peptide mimetics of natural GPCR receptor ligands, peptide and non-peptide allosteric effectors of GPCR receptors, and peptides that may function as activators or inhibitors (competitive, uncompetitive and non-competitive) (e.g., antibody products) of GPCR receptors. The invention does not restrict the sources for suitable modulators, which may be obtained from natural sources such as plant, animal or mineral extracts, or non-natural sources such as small molecule libraries, including the products of combinatorial chemical approaches to library construction, and peptide libraries. Examples of peptide modulators of GPCR receptors exhibit the following primary structures:

GLGPRPLRFamide, GNSFLRFamide, GGPQGPLRFamide, GPSGPLRFamide, PDVDHVFLRFamide, and pyro- EDVDHVFLRFamide.

Other assays can be used to examine enzymatic activity including, but not limited to, photometric, radiometric, BPLC, electrochemical, and the like, which are described in, for example, *Enzyme Assays: A Practical Approach*, eds. R. Eisinger and M. J. Danson, 1992, Oxford University Press, which is incorporated herein by reference in its entirety.

The use of cDNAs encoding GPCRs in drug discovery programs is well- known; assays capable of testing thousands of unknown compounds per day in high- throughput screens (HTSs) are thoroughly documented. The literature is replete with examples of the use of radiolabelled ligands in HTS binding assays for drug discovery (see Williams, 5 Medicinal Research Reviews, 1991, 11, 147-184; Sweetnam, et al., J Natural Products, 1993, 56, 441- 455 for review).

Recombinant receptors are preferred for binding assay HTS because they allow for better specificity (higher relative purity), provide the ability to generate large amounts of receptor material, and can be used in a broad variety of formats (see Hodgson, 10 Bio/Technology, 1992, 10, 973-980; each of which is incorporated herein by reference in its entirety).

A variety of heterologous systems is available for functional expression of recombinant receptors that are well known to those skilled in the art. Such systems include bacteria (Strosberg, et al., Trends in Pharmacological Sciences, 1992, 13, 95-98), yeast 15 (Pausch, Trends in Biotechnology, 1997, 15, 487-494), several kinds of insect cells (Vanden Broeck, Int. Rev. Cytology, 1996, 164, 189-268), amphibian cells (Jayawickreme et al., Current Opinion in Biotechnology, 1997, 8, 629-634) and several mammalian cell lines (CHO, HEK293, COS, etc.; see Gerhardt, et al., Eur. J. Pharmacology, 1997, 334, 1-23). These examples do not preclude the use of other possible cell expression systems, including 20 cell lines obtained from nematodes.

In preferred embodiments of the invention, methods of screening for compounds that modulate GPCR activity comprise contacting test compounds with GPCR and assaying for the presence of a complex between the compound and GPCR. In such assays, the ligand is typically labeled. After suitable incubation, free ligand is separated from that present in 25 bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular compound to bind to GPCR.

It is well known that activation of heterologous receptors expressed in recombinant systems results in a variety of biological responses, which are mediated by G proteins expressed in the host cells. Occupation of a GPCR by an agonist results in exchange of 30 bound GDP for GTP at a binding site on the G alpha subunit; one can use a radioactive,

non-hydrolyzable derivative of GTP, GTP γ [35S], to measure binding of an agonist to the receptor (Sim et al., *Neuroreport*, 1996, 7, 729-733). One can also use this binding to measure the ability of antagonists to bind to the receptor by decreasing binding of GTP γ [35S] in the presence of a known agonist.

5 The G proteins can be intact or chimeric. Often, a nearly universally competent G protein (e.g., G16) is used to couple any given receptor to a detectable response pathway. G protein activation results in the stimulation or inhibition of other native proteins, events that can be linked to a measurable response. Examples of such biological responses include, but are not limited to, the following: the ability to survive in the absence of a limiting nutrient in
10 specifically engineered yeast cells (Pausch, *Trends in Biotechnology*, 1997, 15, 487-494); changes in intracellular Ca²⁺ concentration as measured by fluorescent dyes (Murphy, et al., *Cur. Opinion Drug Disc. Dev.*, 1998, 1, 192-199). Fluorescence changes can also be used to monitor ligand-induced changes in membrane potential or intracellular pH; an automated system suitable for HTS has been described for these purposes (Schroeder, et al.,
15 *J Biomolecular Screening*, 1996, 1, 75-80).

Melanophores prepared from *Xenopus laevis* show a ligand-dependent change in pigment organization in response to heterologous GPCR activation; this response is adaptable to HTS formats (Jayawickreme et al., *Cur. Opinion Biotechnology*, 1997, 8, 629-634). Assays are also available for the measurement of common second messengers,
20 including cAMP, phosphoinositides and arachidonic acid, but these are not generally preferred for HTS.

Preferred methods of HTS employing these receptors include permanently transfected CHO cells, in which agonists and antagonists can be identified by the ability to specifically alter the binding of GTP γ [35S] in membranes prepared from these cells. In
25 another embodiment of the invention, permanently transfected CHO cells could be used for the preparation of membranes which contain significant amounts of the recombinant receptor proteins; these membrane preparations would then be used in receptor binding assays, employing the radiolabelled ligand specific for the particular receptor. Alternatively, a functional assay, such as fluorescent monitoring of ligand-induced changes in internal
30 calcium concentration or membrane potential in permanently transfected CHO cells

containing each of these receptors individually or in combination would be preferred for HTS. Equally preferred would be an alternative type of mammalian cell, such as HEK293 or COS cells, in similar formats. More preferred would be permanently transfected insect cell lines, such as *Drosophila* S2 cells. Even more preferred would be recombinant yeast cells expressing the *Drosophila melanogaster* receptors in HTS formats well known to those skilled in the art (e.g., Pausch, Trends in Biotechnology, 1997, 15, 487-494).

The invention contemplates a multitude of assays to screen and identify inhibitors of ligand binding to GPCR receptors. In one example, the GPCR receptor is immobilized and interaction with a binding partner is assessed in the presence and absence of a candidate modulator such as an inhibitor compound. In another example, interaction between the GPCR receptor and its binding partner is assessed in a solution assay, both in the presence and absence of a candidate inhibitor compound. In either assay, an inhibitor is identified as a compound that decreases binding between the GPCR receptor and its binding partner.

Still other candidate inhibitors contemplated by the invention can be designed and include soluble forms of binding partners, as well as such binding partners as chimeric, or fusion, proteins. A "binding partner" as used herein broadly encompasses non-peptide modulators, as well as such peptide modulators as neuropeptides other than natural ligands, antibodies, antibody fragments, and modified compounds comprising antibody domains that are immunospecific for the expression product of the identified GPCR gene.

Compounds may be identified which exhibit similar properties to the ligand for the GPCR of the invention, but which are smaller and exhibit a longer half time than the endogenous ligand in a human or animal body. When an organic compound is designed, a molecule according to the invention is used as a "lead" compound. The design of mimetics to known pharmaceutically active compounds is a well-known approach in the development of pharmaceuticals based on such "lead" compounds. Mimetic design, synthesis and testing are generally used to avoid randomly screening a large number of molecules for a target property.

Furthermore, structural data deriving from the analysis of the deduced amino acid sequences encoded by the DNAs of the present invention are useful to design new drugs, more specific and therefore with a higher pharmacological potency.

The present invention also encompasses a method of agonizing (stimulating) or antagonizing a GPCR natural binding partner associated activity in a mammal comprising administering to said mammal an agonist or antagonist to one of the above disclosed polypeptides in an amount sufficient to effect said agonism or antagonism. One embodiment of the present invention, then, is a method of treating diseases in a mammal with an agonist or antagonist of the protein of the present invention comprises administering the agonist or antagonist to a mammal in an amount sufficient to agonize or antagonize GPCR-associated functions.

Methods for the Identification of GPCR Modulators

Set forth below are several nonlimiting methods for identifying modulators (agonists and antagonists) of GPCR activity. Among the modulators that can be identified by these assays are natural ligand compounds of the receptor; synthetic analogs and derivatives of natural ligands; antibodies, antibody fragments, and/or antibody-like compounds derived from natural antibodies or from antibody-like combinatorial libraries; and/or synthetic compounds identified by high-throughput screening of libraries; and the like. All modulators that bind GPCRs are useful for identifying GPCRs in tissue samples (e.g., for diagnostic purposes, pathological purposes, and the like). Agonist and antagonist modulators are useful for up-regulating and down-regulating GPCR activity, respectively, to treat disease states characterized by abnormal levels of GPCR activity. The assays may be performed using single putative modulators, and/or may be performed using a known agonist in combination with candidate antagonists (or visa versa).

A. cAMP Assays

In one type of assay, levels of cyclic adenosine monophosphate (cAMP) are measured in GPCR-transfected cells that have been exposed to candidate modulator compounds. Protocols for cAMP assays have been described in the literature (See, e. g., Sutherland et al, *Circulation* 37: 279 (1968); Frandsen et al, *Life Sciences* 18: 529-541 (1976); Dooley et al, *Journal of Pharmacology and Experimental Therapeutics* 283 (2): 735-41 (1997); and George et al, *Journal of Biomolecular Screening* 2 (4): 235-40 (1997)). An exemplary protocol for such an assay, using an Adenylyl Cyclase Activation FlashPlate Assay from NENTm Life Science Products, is set forth below.

Briefly, the GPCR coding sequence (e.g., a cDNA or intronless genomic DNA) selected from the group consisting of sequences listed in Table 1, is subcloned into a commercial expression vector, such as pzeoSV2 (Invitrogen), and transiently transfected into Chinese Hamster Ovary (CHO) cells using known methods, such as the transfection
5 protocol provided by Boehringer-Mannheim when supplying the FuGENE 6 transfection reagent. Transfected CHO cells are seeded into 96-well microplates from the FlashPlate (which are coated with solid scintillant to which antisera to cAMP has been bound). For a control, some wells are seeded with wild type (untransfected) CHO cells. Other wells in the plate receive various amounts of a cAMP standard solution for use in creating a
10 standard curve.

One or more test compounds (i.e., candidate modulators) are added to the cells in each well, with water and/or compound-free medium/diluent serving as a control or controls. After treatment, cAMP is allowed to accumulate in the cells for exactly 15 minutes at room temperature. The assay is terminated by the addition of lysis buffer containing
15 labeled cAMP, and the plate is counted using a Packard Topcount™ 96-well microplate scintillation counter. Unlabeled cAMP from the lysed cells (or from standards) and fixed amounts of cAMP compete for antibody bound to the plate. A standard curve is constructed, and cAMP values for the unknowns are obtained by interpolation. Changes in intracellular cAMP levels of cells in response to exposure to a test compound are indicative of GPCR
20 modulating activity.

Modulators that act as agonists of receptors which couple to certain G proteins will stimulate production of cAMP, leading to a measurable 3 -10 fold increase in cAMP levels. Agonists of receptors which couple to the Gi/z subtype of G proteins will inhibit forskolin stimulated cAMP production, leading to a measurable decrease in cAMP levels of 50-100%.
25 Modulators that act as inverse agonists will reverse these effects at receptors that are either constitutively active or activated by known agonists.

GPCR modulators that act as agonists at receptors which couple to the Gs subtype of G proteins will activate adenylyl cyclase leading to a 3-10 fold increase in cyclic adenosine monophosphate (cAMP). Compounds to be tested for the ability to activate GPCR were

assayed for cAMP using an Adenylyl Cyclase Activation FlashPlate® Assay from NENTm Life Science Products.

In a similar assay to measure cAMP release, a GPCR cDNA is subcloned into the commercial expression vector pCMVSPORT (Gibco/Life Technologies) and transiently
5 transfected into CHO or COS 7 cells using the transfection reagent FuGENE 6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert. 24 hours post transfection the cells are harvested by dislodging from the culture flask using Versene (Gibco/BRL). The cells are counted and prepared as a suspension in a buffer included in the assay kit that contains the phosphodiesterase inhibitor isobutylmethylxanthine. The assay is
10 conducted in a special 96 well microplate included in the kit which is coated with solid scintillant to which antisera to cAMP has been bound. Dilutions of test compounds to be tested for activation of GPCR are added to assay wells. Several wells on the plate receive various amounts of cAMP standard solution. After the addition of cells transiently expressing GPCR, cAMP is allowed to accumulate for exactly 15 minutes at room
15 temperature. The assay is terminated by the addition of lysis buffer containing labelled cAMP, and the plate is covered and allowed to incubate at room temperature for 2-24 hours. The plate is then counted using a Packard Topcount™ 96-well microplate scintillation counter.

Unlabelled cAMP from cells (or standards) competes with fixed amounts of labelled
20 cAMP for antibody bound to the plate. A standard curve is constructed and CAMP values for the unknowns are obtained by interpolation. Data were analyzed using GraphPad Prism (San Diego, CA).

B. Aequorin Assays

In another assay, cells (e.g., CHO cells) are transiently co- transfected with both a
25 GPCR expression construct and a construct that encodes the photoprotein apoaequorin. In the presence of the cofactor coelenterazine, apoaequorin will emit a measurable luminescence that is proportional to the amount of intracellular (cytoplasmic) free calcium (Cobbold, et al. "Aequorin measurements of cytoplasmic free calcium," In: McCormack J.G. and Cobbold P.H., eds., Cellular Calcium: A Practical Approach. Oxford: IRL Press (1991); Stables et
30 al., Analytical Biochemistry 252: 115-26 (1997); and Haugland, Handbook of Fluorescent

Probes and Research Chemicals, Sixth edition. Eugene OR: Molecular Probes (1996)). In one exemplary assay, GPCR is subcloned into the commercial expression vector pzeoSV2 (Invitrogen) and transiently co-transfected along with a construct that encodes the photoprotein apoaequorin (Molecular Probes, Eugene, OR) into CHO cells using the
5 transfection reagent FuGENE 6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert.

The cells are cultured for 24 hours at 37C in MEM (Gibco/BRL, Gaithersburg, MD) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin, at which time the medium is changed to serum-free MEM containing
10 coelenterazine (Molecular Probes, Eugene, OR). Culturing is then continued for two additional hours at 37C. Subsequently, cells are detached from the plate using VERSEN (Gibco/BRL), washed, and resuspended at 200,000 cells/ml in serum free MEM.

Dilutions of candidate GPCR modulator compounds are prepared in serum free MEM and dispensed into wells of an opaque 96-well assay plate. Plates are then loaded
15 onto an MLX microtiter plate luminometer (Dynex Technologies, Inc., Chantilly, VA). The instrument is programmed to dispense cell suspensions into each well, one well at a time, and immediately read luminescence for 15 seconds. Dose-response curves for the candidate modulators are constructed using the area under the curve for each light signal peak. Data are analyzed with SlideWrite, using the equation for a one-site ligand, and EC50 values are
20 obtained. Changes in luminescence caused by the compounds are considered indicative of modulatory activity. Modulators that act as agonists at receptors which couple to the Gq subtype of G proteins give an increase in luminescence of up to 100 fold. Modulators that act as inverse agonists will reverse this effect at receptors that are either constitutively active or activated by known agonists. GPCR agonist activation of receptors that couple to
25 the Gq subtype of G proteins will lead to the release of intracellular calcium. The photoprotein aequorin emits a characteristic luminescence in the presence of calcium and may be expressed in cells along with the receptor of interest in order to report agonist signalling.

Briefly, GPCR cDNA selected from the group consisting of sequences listed in
30 Table 1, is subcloned into the commercial expression vector pCMVSPORT (Gibco/Life

Technologies) and transiently transfected along with an Aequorin expression construct (Molecular Probes, Eugene, OR) into COS 7 cells using the transfection reagent FuGENE 6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert. 24 hours post transfection the cells are harvested by dislodging from the culture flask using Versene (Gibco/BRL) and prepared as a suspension in assay buffer (Dulbecco's Modified Eagle's Medium with high glucose, pyridoxine HCl, L- glutamine, sodium pyruvate, and 0.1 % fetal bovine serum (Gibco/BRL)) and containing the cofactor coelenterazine (Molecular Probes). The cell suspension is incubated for 4 hours at room temperature with gentle stirring. After the coelenterazine loading incubation, the cells are counted and diluted to 1,000,000 cells/ml in assay buffer. Dilutions of test compound are prepared in assay buffer and pipetted into wells of an opaque 96-well assay plate. Plates are loaded onto an MLX microtiter plate luminometer (Dynex Technologies, Chantilly, VA). The instrument is programmed to dispense cell suspension into each well, one well at a time, and immediately read luminescence for 20 seconds. Dose response curves are constructed using the area under the curve for each light signal peak

Luciferase Reporter Gene Assay

The photoprotein luciferase provides another useful tool for assaying for modulators of GPCR activity. Cells (e.g., CHO cells or COS 7 cells) are transiently co-transfected with both a GPCR expression construct (e.g., GPCR in pzeoSV2) and a reporter construct which includes a gene for the luciferase protein downstream from a transcription factor binding site, such as the cAMP-response element (CRE), AP-1, or NF-kappa B. Agonist binding to receptors coupled to the G_i subtype of G proteins leads to increases in cAMP, thereby activating the CRE transcription factor and resulting in expression of the luciferase gene. Agonist binding to receptors coupled to the G_q subtype of G protein leads to production of diacylglycerol that activates protein kinase C, which activates the AP-1 or NF-kappa B transcription factors, in turn resulting in expression of the luciferase gene. Expression levels of luciferase reflect the activation status of the signaling events (George et al., *Journal of Biomolecular Screening*, 2(4): 235-240 (1997); and Stratowa et al., *Current Opinion in Biotechnology* 6: 574-581 (1995)). Luciferase activity may be quantitatively measured

using, e.g., luciferase assay reagents that are commercially available from Promega (Madison, WI).

In one exemplary assay, CHO cells are plated in 24-well culture dishes at a density of 100,000 cells/well one day prior to transfection and cultured at 37°C in MEM

5 (Gibco/13RL) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 Lg/ml streptomycin. Cells are transiently co-transfected with both a GPCR expression construct and a reporter construct containing the luciferase gene. The reporter plasmids CRE-luciferase, AP1 -luciferase and NF-kappaB-luciferase may be purchased from Stratagene (LaJolla, CA).

10 Transfections are performed using the FuGENE 6 transfection reagent (Boehringer-Mannheim) according to the supplier's instructions. Cells transfected with the reporter construct alone are used as a control. Twenty-four hours after transfection, cells are washed once with PBS pre-warmed to 37°C. Serum-free MEM is then added to the cells either alone (control) or with one or more candidate modulators and the cells are incubated at
15 37°C for five hours. Thereafter, cells are washed once with ice-cold PBS and lysed by the addition of lysis buffer from the luciferase assay kit supplied by Promega. After incubation for 15 minutes at room temperature, lysate is mixed with substrate solution (Promega) in an opaque-white, 96-well plate, and the luminescence is read immediately on a Wallace model 1450 MicroBeta scintillation and luminescence counter (Wallace Instruments, Gaithersburg,
20 MD). Differences in luminescence in the presence versus the absence of a candidate modulator compound are indicative of modulatory activity. Receptors that are either constitutively active or activated by agonists typically give a 3 to 20-fold stimulation of luminescence compared to cells transfected with the reporter gene alone. Modulators that act as inverse agonists will reverse this effect.

25 C. Intracellular calcium measurement using FLIPR

Changes in intracellular calcium levels are another recognized indicator of G protein- coupled receptor activity, and such assays can be employed to screen for modulators of GPCR activity. For example, CHO cells stably transfected with a GPCR expression vector are plated at a density of 40,000 cells/well in 96-well plates specially
30 designed to discriminate fluorescence signals emanating from the various wells on the plate.

The cells are incubated for 60 minutes at 37°C in modified Dulbecco's PBS containing pyruvate and 1 g/L glucose with the addition of 1% fetal bovine serum and one of four calcium indicator dyes (Fluo-3Tm AM, Fluo-4Tm AM, Calcium GreenTm-1 AM, or Oregon GreenTm BAPTA-1 AM). Plates are washed once with modified Dulbecco's PBS
5 without 1% fetal bovine serum and incubated for 10 minutes at 37°C to remove residual dye from the cellular membrane. In addition, a series of washes with modified Dulbecco's PBS without fetal bovine serum is performed immediately prior to activation of the calcium response. A calcium response is initiated by the addition of one or more candidate receptor agonist compounds, calcium ionophore A23187 (positive control), or ATP (positive
10 control). Fluorescence is measured by Molecular Device's FLIPR with an argon laser (excitation 144 at 488 nm) (Kuntzweiler et al., Drug Development Research, 44(1):14-20 (1998)).

Basal fluorescence of cells was measured for 20 seconds prior to addition of candidate agonist, ATP, or A23187, and the basal fluorescence level was subtracted from
15 the response signal. The calcium signal is measured for approximately 200 seconds, taking readings every two seconds. Calcium ionophore A23187 and ATP increase the calcium signal 200% above baseline levels. In general, activated GPCRs increase the calcium signal approximately 10-15% above baseline signal.

GPCR HEK293 cells were transiently transfected with an expression vector
20 containing the nucleic acid of a GPCR selected from the group consisting of sequences listed in Table 1 and empty vector using Lipofectamine plus (Gibco) according to the manufacturer's instructions. The next day, the cells were seeded into 96-well plates at 25,000 cells per well. The following day, cells were loaded with 1 uM Fluo-4-acetoxymethyl fluorescent indicator dye (Molecular Probes) in MEM (minimal essential
25 media) containing 0.1 % bovine serum albumin, 0.04% pluronic acid and 2.5 mM probenecid for 30 minutes at 37°C. The cells were washed with pre-warmed (37°C) assay buffer (Hanks buffer containing 15 mM HEPES, 2.5 mM probenecid and 0.1 % bovine serum albumin). Assay buffer (100 ul) was added to each well and plates were incubated at 37°C for 15 minutes. Various concentrations (0.03 pM-10 nM) of human Peptide A or

salmon Peptide B were added and fluorescence produced by fluo-4 (a calcium sensitive dye) was measured every second for 150 seconds on a fluorometric imaging plate reader (FLIPR; Molecular Devices).

E. Mitogenesis Assay

- 5 In a mitogenesis assay, the ability of candidate modulators to induce or inhibit GPCR mediated cell division is determined (See, e.g., Lajiness et al., Journal of Pharmacology and Experimental Therapeutics 267(3): 1573-1581 (1993)). For example, CHO cells stably expressing GPCR are seeded into 96-well plates at a density of 5000 cells/well and grown in MEM with 10% fetal calf serum for 48 hours, at which time the cells are
- 10 rinsed twice with serum-free MEM. After rinsing, fresh MEM, or MEM containing a known mitogen, is added along with MEM containing varying concentrations of one or more candidate modulators or test compounds diluted in serum-free medium. As controls, some wells on each plate receive serum-free medium alone, and some receive medium containing 10% fetal bovine serum. Untransfected cells or cells transfected with vector alone also may
- 15 serve as controls. After culture for 16-18 hours, [3H]-thymidine is added to the wells and cells are incubated for an additional 2 hours at 37°C. The cells are trypsinized and collected on filter mats with a cell harvester, the filters are then counted in a Betaplate counter. The incorporation of [3H]-thymidine in serum-free test wells is compared to the results achieved in cells stimulated with serum (positive control). Use of multiple concentrations of test
- 20 compounds permits creation and analysis of dose-response curves using the non-linear, least squares fit equation: $A = B \times [C / (D + C + G)]$ where A is the percent of serum stimulation; B is the maximal effect minus baseline; C is the EC50; D is the concentration of the compound; and G is the maximal effect. Parameters B, C and G are determined by Simplex optimization. Agonists that bind to the receptor are expected to increase [3H]-thymidine
- 25 incorporation into cells, showing up to 80% of the response to serum. Antagonists that bind to the receptor will inhibit the stimulation seen with a known agonist by up to 100%.

D. GTP γ S binding assay

- Because G protein-coupled receptors signal through intracellular G proteins whose activity involves GTP binding and hydrolysis to yield bound GDP, measurement of binding
- 30 of the non-hydrolyzable GTP analog [35S]-GTP γ S in the presence and absence of candidate

modulators provides another assay for modulator activity (See, e.g., Kowal et al., Neuropharmacology 37:179-187 (1998)). In one exemplary assay, cells stably transfected with a GPCR expression vector are grown in 10 cm tissue culture dishes to subconfluence, rinsed once with 5 ml of ice-cold $\text{Ca}^{2+}/\text{Mg}^{2+}$ -free phosphate-buffered saline, and scraped
5 into 5 ml of the same buffer. Cells are pelleted by centrifugation ($500 \times g$, 5 minutes), resuspended in TEE buffer (25 mM Tris, pH 7.5, 5 mM EDTA, 5 mM EGTA), and frozen in liquid nitrogen. After thawing, the cells are homogenized using a Dounce homogenizer (one ml TEE per plate of cells), and centrifuged at $1,000 \times g$ for 5 minutes to remove nuclei and unbroken cells.

10 The homogenate supernatant is centrifuged at $20,000 \times g$ for 20 minutes to isolate the membrane fraction, and the membrane pellet is washed once with TEE and resuspended in binding buffer (20 mM HEPES, pH 7.5, 150 mM NaCl, 10 mM MgCl_2 , 1 mM EDTA). The resuspended membranes can be frozen in liquid nitrogen and stored at -70°C until use. Aliquots of cell membranes prepared as described above and stored at -70°C are thawed,
15 homogenized, and diluted. Final homogenates are incubated with varying concentrations of candidate modulator compounds or GTP for 30 minutes at 30°C and then placed on ice. To each sample, guanosine 5'-O-(3 [35S thio] triphosphate (NEN, 1200 Ci/mmol; [35S]-GTP γ S), was added to a final concentration of 100-200 pM. Samples are incubated at 30°C for an additional 30 minutes, 1 ml of 10mM HEPES, pH 7.4, 10 mM MgCl_2 , at 4°C is added
20 and the reaction is stopped by filtration.

Samples are filtered over Whatman GF/B filters and the filters are washed with 20 ml ice-cold 10 mM HEPES, pH 7.4, 10 mM MgCl_2 . Filters are counted by liquid scintillation spectroscopy. Nonspecific binding of [35S]-GTP γ S is measured in the presence of GTP and subtracted from the total. Compounds are selected that modulate the amount of
25 [35S]-GTP γ S binding in the cells, compared to untransfected control cells. Activation of receptors by agonists gives up to a five-fold increase in [35S] GTP γ S binding. This response is blocked by antagonists.

E. MAP Kinase Activity Assay

Evaluation of MAP kinase activity in cells expressing a GPCR provides another assay to identify modulators of GPCR activity (Lajiness et al., Journal of Pharmacology and Experimental Therapeutics 267(3):1573-1581 (1993) and Boulton et al., Cell 65: 663-675 (1991)). In one embodiment, CHO cells stably transfected with GPCR are seeded into 6-
5 well plates at a density of 70,000 cells/well 48 hours prior to the assay. During this 48-hour period, the cells are cultured at 37C in MEM medium supplemented with 10% fetal bovine serum, 2mM glutamine, 10 U/ml penicillin and streptomycin. The cells are serum-starved for 1-2 hours prior to the addition of stimulants.

For the assay, the cells are treated with medium alone or medium containing either a
10 candidate agonist or 200 nM Phorbol ester-myristoyl acetate (i.e., PMA, a positive control), and the cells are incubated at 37C for varying times. To stop the reaction, the plates are placed on ice, the medium is aspirated, and the cells are rinsed with 1 ml of ice-cold PBS containing EDTA. Thereafter, cell lysis buffer is added to the cells. The cells are scraped from the plates and homogenized by 10 passages through a 23G needle, and the cytosol
15 fraction is prepared by centrifugation at 20,000 x g for 15 minutes. Aliquots of cytosol are mixed with MAPK Substrate Peptide (APRTPGGRR), Upstate Biotechnology, Inc., N.Y.) and [γ -32 P] ATP (NEN, 3000 Ci/mmol), diluted to a final specific activity of 2000 cpm/pmol. The samples are incubated for 5 minutes at 30C, and reactions are stopped by spotting on Whatman P81 phosphocellulose paper. The filter squares are washed and are
20 subjected to liquid scintillation spectroscopy to quantitate bound label. Equivalent cytosolic extracts are incubated without MAPK substrate peptide, and the bound label from these samples are subtracted from the matched samples with the substrate peptide. The cytosolic extract from each well is used as a separate point. Protein concentrations are determined by a dye binding protein assay (Bio-Rad Laboratories). Agonist activation of the receptor is
25 expected to result in up to a five-fold increase in MAPK enzyme activity. This increase is blocked by antagonists.

F. Arachidonic Acid Release

The activation of GPCRs also has been observed to potentiate arachidonic acid release in cells, providing yet another useful assay for modulators of GPCR activity
30 (Kanterman et al., Molecular Pharmacology 3 9:3 64-3 69 (199 1)). For example, CHO cells

that are stably transfected with a GPCR expression vector are plated in 24 well plates at a density of 15,000 cells/well and grown in MEM medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and streptomycin for 48 hours at 37C before use. Cells of each well are labeled by incubation with [3H]-arachidonic acid
5 (Amersham Corp., 210 Ci/mmol) for 2 hours at 37C. The cells are then washed twice with 1 ml of buffer. Candidate modulator compounds are added in 1 ml of the same buffer, either alone or with ATP and the cells are incubated at 37C for 30 minutes. Buffer alone and mock transfected cells are used as controls. Samples (0.5 ml) from each well are counted by liquid scintillation spectroscopy. Agonists which activate the receptor will lead to potentiation of
10 the ATP-stimulated release of [3H]-arachidonic acid. This potentiation is blocked by antagonists.

G. Extracellular Acidification Rate

In yet another assay, the effects of candidate modulators of GPCR activity are assayed by monitoring extracellular changes in pH induced by the test compounds (See,
15 e.g., Dunlop et al., Journal of Pharmacological and Toxicological Methods 40(1):47-55 (1998)). In one embodiment, CHO cells transfected with a GPCR selected from the group consisting of sequences listed in Table 1 in an expression vector are seeded into 12 min capsule cups (Molecular Devices Corp.) at 400,000 cells/cup in MEM supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10 U/ml penicillin, and 10 µg/ml
20 streptomycin. The cells are incubated in this medium at 37C in 5% CO₂ for 24 hours. Extracellular acidification rates are measured using a Cytosensor microphysiometer (Molecular Devices Corp.). Candidate agonists or other agents are diluted into the running buffer and perfused through a second fluid path. The pH of the running buffer in the sensor chamber is recorded during the cycle from 43-58 seconds, and the pump is re-started at 60
25 seconds to start the next cycle. The rate of acidification of the running buffer during the recording time is calculated by the Cytosoft program. Changes in the rate of acidification are calculated by subtracting the baseline value (the average of 4 rate measurements immediately before addition of a modulator candidate) from the highest rate measurement obtained after addition of a modulator candidate. Modulators that act as agonists of the
30 receptor result in an increase in the rate of extracellular acidification compared to the rate in

the absence of agonist. This response is blocked by modulators which act as antagonists of the receptor.

H. Radio ligand Binding Assay

HEK 293 or COS7 cells transiently expressing or CHO K-1 cells stably expressing a GPCR selected from the group consisting of sequences listed in Table 1, were grown to sub-confluence, harvested from flasks in Dulbecco's PBS and pelleted. Cell pellets were homogenized in 10 ml tissue buffer using a dounce, 10 strokes. Homogenate was centrifuged at 47,000 x g for 15 minutes. Membrane pellet was resuspended in 1 ml tissue buffer using the dounce, 10 strokes. An aliquot of the membrane preparation was used to determine protein concentration. For measurement of saturation binding, Cell membranes were incubated with various concentrations of labelled agonist Peptide (iodinated by routine procedures via the Tyr residue) in binding assay buffer for 90 minutes at room temperature in 96-well plates. Non-specific binding was defined by the inclusion of unlabeled agonist Peptide. After the binding incubation, plates were harvested onto GF/C filters presoaked in 0.3% non-fat dry milk. Filters were dried, and counted in a 96-well microplate scintillation counter. Data were analyzed using GraphPad Prism (San Diego, CA) and Kd values were calculated.

Identification of natural GPCR ligands

Isolated GPCRs can be used to isolate novel or known ligands (Saito et al., Nature, 400: 265-269, 1999). The cDNAs that encode the isolated GPCR selected from the group consisting of sequences listed in Table 1, can be cloned into mammalian expression vectors and used to stably or transiently transfect mammalian cells including CHO, Cos or HEK293 cells. Receptor expression can be determined by Northern blot analysis of transfected cells and identification of an appropriately sized mRNA band (predicted size from the cDNA) or PCR. Tissues shown by mRNA analysis to express each of the GPCR proteins could be processed for ligand extraction using any of several protocols ((Reinsheidk R.K. et al., Science 270: 243-247, 1996; Sakurai, T., et al., Cell 92; 573-585, 1998; Hinuma, S., et al., Nature 393: 272-276, 1998). Chromatographic fractions of brain extracts could be tested for ability to activate GPCR proteins by measuring second messenger production such as changes in cAMP production in the presence or absence of forskolin, changes in inositol 3-

phosphate levels, changes in intracellular calcium levels or by indirect measures of receptor activation including receptor stimulated mitogenesis, receptor mediated changes in extracellular acidification or receptor mediated changes in reporter gene activation in response to cAMP or calcium (these methods are referenced in other sections of the patent).

- 5 Receptor activation could also be monitored by co-transfecting cells with a chimeric Gq/i3 to force receptor coupling to a calcium stimulating pathway (Conklin et al., Nature 363; 274-276, 1993). Ligand mediated activation of receptors could also be monitored by measuring changes in [35S]-GTP γ S binding in membrane fractions prepared from transfected mammalian cells. This assay could also be performed using baculoviruses
10 containing GPCR proteins infected into SF9 insect cells.

The ligand which activates GPCR proteins can be purified to homogeneity through successive rounds of purification using GPCR proteins activation as a measurement of neurotransmitter activity. The composition of the ligand can be determined by mass spectrometry and other methods. Ligands isolated in this manner will be bioactive materials
15 which will affect physiological processes.

Protein Interaction Assays

- Protein interaction assays may also be utilized to identify GPCR modulator compounds. To carry out such an assay, a GPCR polypeptide of the invention (or a
20 polypeptide fragment thereof or an epitope-tagged form or fragment thereof) is harvested from a suitable source (e.g., from a prokaryotic expression system, eukaryotic cells, a cell-free system, or by immunoprecipitation from GPCR polypeptide-expressing cells). The GPCR polypeptide is then bound to a suitable support (e.g., nitrocellulose or an antibody or a metal agarose column in the case of, for example, a his-tagged form of a GPCR
25 polypeptide). Binding to the support is preferably done under conditions that allow polypeptides associated with a GPCR polypeptide to remain associated with it. Such conditions may include use of buffers that minimize interference with protein-protein interactions. The binding step can be done in the presence and absence of compounds being tested for their ability to interfere with interactions between a GPCR polypeptide of the
30 invention and other molecules. If desired, other proteins (e.g., a cell lysate) are added, and

allowed time to associate with the polypeptide. The immobilized GPCR polypeptide is then washed to remove proteins or other cell constituents that may be non-specifically associated with the polypeptide or the support. The immobilized GPCR polypeptide is then dissociated from its support, and so that proteins bound to it are released (for example, by heating), or alternatively, associated proteins are released from the GPCR polypeptide without releasing the GPCR polypeptide from the support. The released proteins and other cell constituents can be analyzed, for example, by SDS-PAGE gel electrophoresis, western blotting and detection with specific antibodies, phosphoamino acid analysis, protease digestion, protein sequencing, or isoelectric focusing. Normal and polymorphic (or mutagenized) forms of a GPCR polypeptide of the invention can be employed in these assays to gain additional information about the part of a GPCR polypeptide to which a given factor binds. In addition, when incompletely purified polypeptide is employed, comparison of the normal and polymorphic forms of the polypeptide can be used to help distinguish true binding proteins.

The proceeding assay can be performed using a purified or semipurified protein or other molecule that is known to interact with a GPCR polypeptide of the invention. This assay may include the following steps.

1. Harvest a GPCR polypeptide of the invention and couple a suitable fluorescent label to it;
2. Label an interacting polypeptide (or other molecule) with a second, different fluorescent label. Use dyes that will produce different quenching patterns when they are in close proximity to each other vs. when they are physically separated (i.e., dyes that quench each other when they are close together but fluoresce when they are not in close proximity);
3. Expose the interacting molecule to the immobilized GPCR polypeptide in the presence or absence of a compound being tested for its ability to interfere with an interaction between the two; and
4. Collect fluorescent readout data.

Another assay includes a Fluorescent Resonance Energy Transfer (FRET) assay. This assay can be performed as follows.

1. Provide a GPCR polypeptide of the invention or a suitable polypeptide fragment thereof and couple a suitable FRET donor (e.g., nitro-benzoxadiazole (NBD)) to it;
2. Label an interacting polypeptide (or other molecule) with a FRET acceptor (e.g., rhodamine);
- 5 3. Expose the acceptor-labeled interacting molecule to the donor-labeled GPCR polypeptide in the presence or absence of a compound being tested for its ability to interfere with an interaction between the two; and
4. Measure fluorescence resonance energy transfer.

10 Quenching and FRET assays are related. Either one can be applied in a given case, depending on which pair of fluorophores is used in the assay.

Interaction Trap/Two-Hybrid System

In order to assay for GPCR-interacting proteins, the interaction trap/two-hybrid
15 library screening method can be used. This assay was first described in Fields et al., *Nature*, 1989, 340, 245, which is incorporated herein by reference in its entirety. A protocol is published in *Current Protocols in Molecular Biology* 1999, John Wiley & Sons, NY, and Ausubel, F. M. et al. 1992, *Short protocols in molecular biology*, Fourth edition, Greene and Wiley-Interscience, NY, each of which is incorporated herein by reference in its
20 entirety. Kits are available from Clontech, Palo Alto, CA (Matchmaker Two-Hybrid System).

A fusion of the nucleotide sequences encoding all or partial GPCR and the yeast transcription factor GAL4 DNA-binding domain (DNA-BD) is constructed in an appropriate plasmid (i.e., pGBKT7) using standard subcloning techniques. Similarly, a
25 GAL4 active domain (AD) fusion library is constructed in a second plasmid (i.e., pGADT7) from cDNA of potential GPCR-binding proteins (for protocols on forming cDNA libraries, see Sambrook et al. 1989, *Molecular cloning: a laboratory manual*, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY), which is incorporated herein by reference in its entirety. The DNA-BD/GPCR fusion construct is verified by sequencing,
30 and tested for autonomous reporter gene activation and cell toxicity, both of which would

prevent a successful two-hybrid analysis. Similar controls are performed with the AD/library fusion construct to ensure expression in host cells and lack of transcriptional activity. Yeast cells are transformed with both the GPCR and library fusion plasmids according to standard procedures (Ausubel et al., 1992, Short protocols in molecular biology, fourth edition, Greene and Wiley-interscience, NY, which is incorporated herein by reference in its entirety). In vivo binding of DNA-BD/GPCR with AD/library proteins results in transcription of specific yeast plasmid reporter genes (i.e., lacZ, HIS3, ADE2, LEU2). Yeast cells are plated on nutrient-deficient media to screen for expression of reporter genes. Colonies are dually assayed for β -galactosidase activity upon growth in Xgal (5-bromo-4-chloro-3-indolyl-p-D-galactoside) supplemented media (filter assay for P-galactosidase activity is described in Breeden et al., Cold Spring Harb. Symp. Quant. Biol., 1985, 50, 643, which is incorporated herein in its entirety). Positive AD library plasmids are rescued from transformants and reintroduced into the original yeast strain as well as other strains containing unrelated DNA-BD fusion proteins to confirm specific GPCR/library protein interactions. Insert DNA is sequenced to verify the presence of an open reading frame fused to GAL4 AD and to determine the identity of the GPCR-binding protein.

Nucleic acid-based assays

Polynucleotides encoding a GPCR polypeptide of the invention may be used in an assay based on the interaction of factors necessary for GPCR gene transcription. The association between the DNA and the binding factor may be assessed by means of any system that discriminates between protein-bound and non-protein-bound DNA (e.g., a gel retardation assay). The effect of a compound on the interaction of a factor to DNA is assessed by means of such an assay. In addition to *in vitro* binding assays, *in vivo* assays in which the regulatory regions of a GPCR polynucleotide are linked to reporter systems can also be performed.

Assays measuring the stability of a GPCR polypeptide

A cell-based or cell-free system can be used to screen for compounds based on their effect on the half-life of GPCR mRNA or polypeptide (Belasco, J. and G. Brawerman.

1993, Control of messenger RNA stability (New York: Academic Press); Ross, J. 1996. Trends in Genetics 12, 171-175; Jacobson, A and S.W. Peltz, 1996. Annu. Rev. Biochem 65, 693-739). The assay may employ labeled mRNA or polypeptide. Alternatively, GPCR mRNA may be detected by means of specifically hybridizing probes or a quantitative PCR
5 assay. Protein can be quantified, for example, by fluorescent or radioactively labeled antibody-based methods. The following represent exemplary assays:

In vitro mRNA stability assay

1. Isolate or produce, by *in vitro* transcription, a suitable quantity of GPCR mRNA;
- 10 2. Label the GPCR mRNA;
3. Expose aliquots of the mRNA to a cell lysate in the presence or absence of a compound being tested for its ability to modulate GPCR mRNA stability; and
4. Assess intactness of the remaining mRNA at suitable time points.

15 *In vitro protein stability assay*

1. Express a suitable amount of a GPCR polypeptide of the invention;
2. Label the polypeptide;
3. Expose aliquots of the labeled polypeptide to a cell lysate in the presence or absence of a compound being tested for its ability to modulate GPCR polypeptide stability;
- 20 and
4. Assess intactness of the remaining polypeptide at suitable time points.

In vivo mRNA or polypeptide stability assay

1. Incubate cells expressing GPCR mRNA or polypeptide with a tracer
25 (radiolabeled ribonucleotide or radiolabeled amino acid, respectively) for a very brief time period (e.g., five minutes) in the presence or absence of a compound being tested for its effect on mRNA or polypeptide stability;
2. Incubate with unlabeled ribonucleotide or amino acid; and
3. Quantify the GPCR mRNA or protein radioactivity at time intervals beginning
30 with the start of step 2 and extending to the time when the radioactivity in GPCR mRNA or

protein has declined by approximately 80%. It is preferable to separate the intact or mostly intact mRNA or protein from its radioactive breakdown products by a means such as hybridization, antibody precipitation, and/or gel electrophoresis in order to quantify the mRNA or protein.

5

Assays measuring inhibition of dominant negative activity

Polymorphic GPCR polypeptides may have dominant negative activity (i.e., activity that interferes with the function of a wild-type GPCR). An assay for a compound that can interfere with such a polymorph may be based on any method of quantifying the normal activity of a GPCR in the presence of the polymorph. For example, a normal GPCR facilitates substrate transport, and a dominant negative polymorph would interfere with this effect. Measurement of the ability of a compound to counteract the effect of a dominant negative polymorph may be based on substrate transport, or on any other normal activity of a wild-type GPCR that was inhibited in the polymorph.

15

Assays measuring phosphorylation

The effect of a compound on phosphorylation of a GPCR polypeptide of the invention can be assayed by methods that quantify phosphates on proteins or that assess the phosphorylation state of a specific residue of a GPCR. Such methods include but are not limited to ^{32}P and ^{33}P labeling and immunoprecipitation, detection with antiphosphoamino acid antibodies (e.g., antiphosphoserine antibodies), phosphoamino acid analysis on 2-dimensional TLC plates, techniques involving mass spectroscopy of fragmented or digested GPCRs (eg. MALDI-TOF), and protease digestion fingerprinting of proteins followed by detection of ^{32}P - or ^{33}P - labeled fragments (Clark WA, Izotova L, Philipova D, Wu W, Lin L, Pestka S. *Biotechniques*. 2002 Oct;Suppl:76-8, 80-7; Boutin JA. *J. Chromatogr B Biomed Appl*. 1996 Sep 20; 684(1-2):179-99.; Bleesing JJ, Fleisher TA. *Cell function-based flow cytometry*. *Semin Hematol*. 2001 Apr; 38(2):169-78.; Wooten MW. *Sci STKE*. 2002 Oct 8; 2002(153)).

Assays measuring other post-translational modifications

30

The effect of a compound on the post-translational modification of a GPCR polypeptide of the invention may be based on any method capable of quantifying that particular modification. For example, effects of compounds on glycosylation may be assayed by treating a GPCR polypeptide with glycosylase and quantifying the amount and
5 nature of carbohydrate released (Adam GC, Sorensen EJ, Cravatt BF. Mol Cell Proteomics, 2002 Oct; 1(10):781-90; Van Noorden CJ, Jonges GN. Histochem J. 1995 Feb; 27(2):101-18).

Animal Model Systems

10 Compounds identified as having activity in any of the above-described assays may be subsequently screened in any available animal model system, including, but not limited to, mice, pigs, and dogs. Test compounds are administered to these animals according to standard methods. Test compounds may also be tested in mice bearing mutations in a gene encoding a GPCR polypeptide. Additionally, compounds may be screened for their ability
15 to modulate the activity of a GPCR polypeptide of the invention and its substrate.

Knock-out mice

An animal, such as a mouse, that has had one or both alleles of a GPCR polypeptide of the invention inactivated (e.g., by homologous recombination or by insertional
20 mutagenesis) is a preferred animal model for screening for compounds that alleviate aberrant behavior or symptoms from a disease or disorder associated with loss of a GPCR activity. The availability of inbred strains of genetically identical mice is of immense value in studying disease. For example, uniformity of mice in an inbred strain permits the assessment of subtle differences in the expression of behavioral traits. As a result, mice can
25 be altered genetically, or bred in different combinations, to study specific behavioral characteristics.

In the mouse, it is possible to perform targeted changes in a gene, such that the altered gene can be passed from one generation to the next. This is accomplished by the use of mouse embryonic stem (ES) cells. These cells can be genetically modified *in vitro* and
30 then implanted into a foster mother, where they develop into embryos and are brought to

term. The resulting offspring are derived from the altered ES cells and carry the introduced genetic modification in their genome.

The most common laboratory procedure performed in ES cells is the elimination, or knock-out (KO), of a specific gene. For this purpose, a mutation inactivating a target gene is introduced into ES cells. These cells are then used to produce mice containing the faulty gene. Since mice, like humans, contain two copies of every gene, one from each parent, the first generation of mice reared from the modified ES cells contains one copy of the mutant gene and one healthy variety. A single round of interbreeding leads to mice with two copies of the mutant gene and the full manifestation of the introduced mutation (knock out mice) or mice born by foster mothers are bred with wild type mice to produce heterozygotes, and these heterozygotes are interbred to produce knock out mice.

Knock-in mice

Instead of deleting a polynucleotide sequence from the mouse genome, it may be desirable to insert a polynucleotide sequence into the mouse genome. This technique, commonly referred to as "knocking in," can be accomplished using many of the methods described for the production of knock-out mice. In some instances, it may be desirable to "knock in" a polynucleotide encoding a human GPCR polypeptide of the invention to replace the polynucleotide encoding the orthologous mouse GPCR polypeptide. The knocked-in polynucleotide may be expressed under the control of the endogenous mouse regulatory sequence, or may have exogenous regulatory sequences.

ES library, screening, and isolation

The methods used to generate a library of ES cells with random gene disruptions and the screening and isolation of ES clones containing a GPCR disruption may be carried out essentially as described in U.S. Patent No. 6,228,639. In brief, to generate a library of ES cells with random gene disruptions, we infected ES cells with a retroviral vector. The vector is designed to inactivate genes in which it gets inserted. The ES cell insertional library is organized in a 3-D matrix of tubes. One copy of the library is stored as viable cells and the other copy is used to isolate DNA. DNA from the library pools is screened by

PCR for the insertions in the genes of interest. The same insertion found by PCR in pools corresponding to the other dimensions of the library matrix determines the 3-D address of the ES clone containing the disrupted gene.

Other methods are known in the art to generate gene disruptions in animals,
5 including homologous recombination, chemical, radiation, and other mutational methods (Shastry, *Mol. Cell Biochem.* 181:163-179, 1998; Shastry, *Experientia* 51:1028-1039, 1995; Zheng et al., *Nucleic Acids Res.* 27:2354-2360, 1999; Knock outda et al., *Hokkaido Igaku Zasshi* 77:151-156, 2002; Babinet et al., *Ann. Acad. Bras. Cienc.* 73:577-580, 2001; Williams, *J. Appl. Physiol.* 88:1119-1126, 2000).

10 In one embodiment, mice having mutations in a gene encoding a GPCR polypeptide of the present invention are made using homologous recombination. Suitable methods and reagents are described, for example, in U.S. Patent Nos. 5,464,764, 5,487,992, 5,612,205, 5,627,059, 5,789,215, and 6,204,061.

15 **Generation of knock-out and knock-in mice**

Knock-out and knock-in mice are produced according to methods well known in the art (see, e.g., *Manipulating the Mouse Embryo. A Laboratory Manual*, 2nd ed. B. Hogan, R. Beddington, F. Constantini, E. Lacy, Cold Spring Harbor Laboratory Press, 1984). In brief, ES cells containing a disrupted GPCR gene are injected into mice blastocysts. These
20 blastocysts are then transferred into uteri of pseudopregnant female mice. Pups born are scored for fur color, and chimeric mice (black and agouti color) with high contribution of agouti fur (50% or more) are tested for germ line transmission by breeding with C57B6/J mice. Presence of agouti progeny indicates germ line transmission, and the same chimera mice are then bred to generate knock-out mice on an inbred background. Alternatively, the
25 chimeric mice are bred directly to 129 mice, and germ line transmission determined by PCR, Southern blotting, or other methods known in the art. The resulting heterozygous mice are then bred to generate knock-out mice on an inbred background.

To generate mice heterozygous for the disrupted GPCR gene (heterozygous knock
outs), the chimera mice are mated with other mice. The progeny from these matings are
30 genotyped by PCR, Southern blotting, or other methods known in the art for the presence of

the knocked out copy of GPCR gene. Knock-out mice homozygous for disruption of the GPCR gene are generated by intercrossing heterozygous mice and genotyping progeny from these crosses.

5 Mice having altered behavior

Behavioral tests may be used to determine the behavioral phenotype of animals (e.g., mice in which one or more GPCR gene of the present invention has been deleted or otherwise modified, and mice overexpressing one or more GPCR polypeptides of the present invention). Suitable tests include, but are not limited to, those that measure behaviors related to anxiety, hyperactivity, hypoactivity, appetite, eating habits, attention, drug abuse, drug addiction, learning and memory, mood, depression, schizophrenia, pain, sleep, arousal, sexuality, and social dominance.

The functional observational battery (FOB) is a series of tests applied to an animal to determine gross sensory and motor deficits. In general, short-duration, non-harmful tactile, olfactory, and visual stimuli are applied to the animal to determine its ability to detect and respond normally to the stimuli. The FOB also provides an opportunity for an investigator to closely observe each animal for skeletal and spontaneous neurological deficits (Crawley et al., *Hormones Behav.* 31:197-211, 1997).

General observational tests include, for example, swim tests, the auditory click test, measurement of body temperature or body weight, the Irwin Observational Test Battery, the olfactory acuity test, and the visual cliff test

One means for measuring animal activity is the home cage activity test. Infrared photobeams provide information of when an animal is moving in its home cage. Animals in their home cages are placed in the photobeam boxes, and data are generated that provide insight into the animal's circadian rhythms activity, as well as general traits of activity (e.g., hypoactivity or hyperactivity) during the testing period.

Another test assays open field activity. Locomotor activity is detected by photobeam breaks as the animal crosses each beam. Measurements used to assess locomotor activity include, for example, total distance traveled, total number of rearing events (animal raises up on hindlimbs), and distance traveled in the center compared to total

distance traveled (center: total distance ratio). Typically, mice are placed in the center of the field. Mice will normally explore the edges/walls first and then, over time, spend more time in the center as they become familiar with the environment. Open field activity determination provides data on the general activity level of mice (i.e. hypo- or hyper-active), as well as an indication of the animal's anxiety-related behaviors in an open-space.

Other means for measuring animal activity include measurement of circadian activity, electroencephalography, electromyography, locomotor activity, novel object exploration, sleep deprivation and sleep rebound after deprivation, susceptibility to acute administration of pharmacological agents in activity and sleep-related tests, susceptibility to chronic administration of pharmacological agents in activity and sleep-related tests, and wheel running activity.

The study of sleep is carried out with the use of the electroencephalograph (EEG) and/or electromyography (EMG). Stereotaxic placement of electrodes onto the cortex for EEG recording and bilateral placement of electrodes into the trapezius muscle in the neck (EMG) allow the different stages of wake and sleep to be analyzed. Animals that display disrupted or altered sleep pattern may serve as models for screening for drugs that treat sleep disorders such as dysomnias and parasomnias.

Tests for determining whether a mouse has altered coordination or movement include the Balance Beam test, Bilateral Tactile Stimulation test, Circling Behavior test, Disengage test, Grip Strength test, Holeboard test, Paw Reaching test, Parallel Bar Walking test, Ring Catalepsy test, Rotorod test, Sterotypy Behavior test, or Vertical Pole test. Coordination and movement can also be assessed by assessment of exercise capacity, footprint pattern, forelimb asymmetry, posture, and gait.

In one example, motor coordination and skill learning is assessed using the rotarod assay, which measures the ability of an animal to maintain balance on an accelerating rotating rod. The mice must walk continuously to avoid falling off (see Crawley et al., *Hormones Behav.* 31:197-211, 1997). Animals are generally given multiple trials spaced at least 20 minutes apart to allow for recovery from any fatigue testing may cause. In general, the time the animal spends walking on top of the rotating rod increases over the trials, thus demonstrating motor coordination and the ability to learn a rudimentary skill. This test

relates to coordination and balance deficiencies.

Feeding and ingestive behaviors can be examined, for example, by monitoring 24 hour food consumption, 24 hour water consumption, body weight during development, circadian feeding patterns, conditioned taste aversion, conditioned taste preference, fasting studies (e.g., weight loss during fasting, weight gain after fasting, feeding response after fasting), liquid intake, macronutrient choice, novel food preference, rebound food consumption response after restricted daily access to food, response to specialized diets (e.g., cafeteria diet, high or low protein diet, high or low fat diet, and high or low carbohydrate diet), susceptibility to acute administration of pharmacological agents in feeding paradigms, and susceptibility to chronic administration of pharmacological agents in feeding paradigms. Food consumption over consecutive days may be determined, e.g., during the monitoring of home cage activity. The amount of consumed food and the body weight of the mouse are determined at various timepoints. If desired, the frequency and duration of eating may also be determined. This assay provides insight into the appetite and eating habits that might relate to eating conditions or disorders.

Sexual responsiveness can be tested, e.g., in a clear chamber with video recording. Male mice are tested to determine if they respond normally to a female mouse. Measurements used to assess normal male responsiveness include, but not limited to, mount latency, mount frequency, pelvic thrusts, intromissions, and ejaculation. Female mice are also tested to determine their sexual receptivity to a male. Measurements used to assess normal female receptivity involve assessing the degree and frequency of lordosis behavior. Sexual behaviors can also be measured by examining sexual motivation, ethologically relevant behaviors (e.g., anogenital investigation) as part of normal social interactions, susceptibility to acute administration of pharmacological agents in sexual responsiveness assays, and susceptibility to chronic administration of pharmacological agents in sexual responsiveness assays. These assays can be used to determine sexual activity in general and to detect any abnormal sexual behavior that might relate to sexual conditions or disorders.

Nociceptive behaviors can be assessed using a test that measures, for example, allodynia as a model for chronic pain, inflammatory pain, pain threshold, sensitivity to

drug-induced analgesia, thermal pain, mechanical pain, chemical pain, hyperalgesia, or shock sensitivity. Particular tests include the allodynia/place avoidance, calibrated von Frey hairs for mechanical pain, cold plate test, cold water tail immersion test, conditioned suppression, formalin paw assay, Hargreaves test, hot plate test, hot water tail immersion test, paw pressure test, paw withdrawal, plantar test, tail flick test, tail pressure test, and the writhing test, susceptibility to acute administration of pharmacological agents in nociception tests, and susceptibility to chronic administration of pharmacological agents in nociception tests. In one example, a mouse's nociception is assessed by placing the mouse on a 55°C hot plate. The latency to a hind limb response (shake or lick) is measured. This assay provides data on the animal's general analgesic response to a thermal stimulus, and is used to detect a nociceptive condition or disorder. The formalin paw assay measures the response to a noxious chemical injected into the hindpaw. Licking and biting of the hindpaw is quantitated as the amount of time engaged in these activities. Two phases of responses are demonstrated with the first phase representing an acute pain response and the second phase representing a hyperalgesic response. Alterations in this normal biphasic display may serve as a model of various forms of pain and chronic pain disorders (Abbott et al., Pain 60:91-102, 1995).

Tests that measure or detect anxiety-related behaviors include acoustic startle habituation, acoustic startle reactivity, active avoidance, the canopy test, conditioned emotional response, conditioned suppression of drinking, conditioned ultrasonic vocalization, dark light emergence task, defensive burying, dPAG-induced flight, elevated plus maze, elevated zero maze, exploration tests in a novel environment, fear-potentiated startle, food exploration test, four plate test, Gellar-Seifter conflict test, light-dark box, light-enhanced startle, marble burying test, mirror chamber, novelty suppressed feeding, pain-induced ultrasonic vocalizations, petition test, passive avoidance, probe burying test, punished locomotion test, separation-induced ultrasonic vocalizations, shock sensitization of startle response, social competition, social interaction, staircase test, susceptibility to acute administration of pharmacological agents in anxiety-related assays, and susceptibility to chronic administration of pharmacological agents in anxiety-related assays. One such test is the light-dark exploration test, which measures the conflict between the natural tendencies

of mice to explore novel environments but to avoid the aversive properties of brightly lit (anxiety-provoking) open areas. In this test, the brightly lit compartment encompasses about two-thirds of the surface area, while the dark compartment encompasses the remaining one-third of the area. An opening is designed to allow the mouse access to both
5 compartments. The mouse is placed at the one end of the brightly lit compartment. The latency to enter the dark compartment, total time spent in the dark compartment, and the number of transitions between the two compartments is measured to give a sense of an anxiety-related response that might be related to an anxiety condition or disorder.

Tests for identifying stress-related behaviors include electric footshock stress tests,
10 handling stress test, maternal separation stress test, restraint induced stress test, sleep deprivation stress test, social isolation stress test, swim stress test, stress-induced hyperthermia, and susceptibility to acute or chronic administration of pharmacological agents in stress-related tasks. These assays provide the ability to study stress and to provide insight into behaviors that may be related to stress conditions or disorders.

15 Tests for identifying fear-related behaviors in rodents include conditioned fear, fear potentiated startle, fear-response behavior, mouse defense test battery, ultrasonic vocalization test, and susceptibility to acute or chronic administration of pharmacological agents in fear-related tests. These assays provide the ability to study emotional based behaviors that may be related to fear-based conditions or disorders.

20 Depression-related tests include acute restraint, chronic restraint, circadian activity, conditioned defensive burying, differential reinforcement to low rate of responding, learned helplessness, Porsolt forced swim test, tail suspension test, sucrose preference test, and susceptibility to acute or chronic administration of pharmacological agents in depression-related tests. Another is the tail suspension test, which includes suspending a mouse by its
25 tail and measuring the duration of time it continues to struggle to escape from an inescapable situation. The time spent struggling is considered a measure of learned helplessness behavior or behavioral despair. The latency to the onset of the end of the struggling can be increased by clinically effective antidepressants. This assay therefore can be used to identify mice that may serve as models for depressive disorders.

Mood related behavioral assays include latent inhibition, marble burying, prepulse inhibition of the acoustic startle response, and susceptibility to acute and chronic administration in mood-related tests. Prepulse inhibition of the acoustic startle response occurs when a loud (120 dB) startle stimulus is preceded by a softer tone that does not elicit a startle response (the prepulse). It is believed that this is a measure of a filtering mechanism in the nervous system that allows an individual to focus on important incoming information and to ignore unimportant information. Schizophrenic patients have been documented to have impaired prepulse inhibition; therefore this test can be used employing mice to identify those having a response that may be indicative of schizophrenia or another psychotic disorder.

Suitable tests for assessing a mouse's learning and memory capacity include, for example, those that measure active avoidance, autoshaping, barnes maze, conditioned taste aversion, conditional spatial alternation, context and auditory cued conditioned fear, contextual discrimination, delayed matching to position, delayed matching/non-matching to position, eyeblink conditioning, fear potentiated startle, figure 8 maze, holeboard test, motor learning using an accelerated rotarod, place aversion test, novel object recognition, olfactory discrimination, passive-avoidance, position/response learning, schedule-induced operant behaviors, radial arm maze, social recognition, social transmission of food preference, step down avoidance, taste learning, temporal processing using the Peak procedure, trace conditioning, T maze avoidance, transverse patterning, visual discrimination, water maze place memory test, vigilance test, and Y maze, and Y maze avoidance.

The Morris water maze test is an assay that measures spatial learning and memory. An animal is trained in a pool of opaque water to locate a platform hidden under the water's surface using spatial cues external cues in the room. Measurements of spatial learning require analysis of spatial selectivity on a probe trial, in which the platform has been removed and the pattern in which the animal searches is examined. An animal that has learned the position of the platform using spatial cues will spend more time in the quadrant where the platform was located, and will also cross the precise location of the platform more often versus other possible sites. This complex learning task provides a way to determine learning and memory deficits and enhancements, and offers insight into the

neural mechanisms of learning and memory (Crawley et al., *Psychopharmacol.* 132:107-124, 1997).

Context and auditory cue fear conditioning (i.e., conditioned fear) is determined by placing a mouse in an enclosed chamber in which the floor is equipped to deliver a mild electrical shock to the mouse's feet. The training day consists of placing the mouse in the chamber and allowing it to explore the environment. At the end of the exploration period, a white noise is turned on (i.e., the conditioning stimulus, CS). A footshock is paired with the white noise turning off. This training trial is then repeated again. At the end of the second trial, the mouse is returned to its home cage. The mouse is tested 24 hours later by separately assaying the amount of freezing exhibited in the context in which it was shocked (Context Test) and the amount of freezing exhibited to the white noise (CS Test). As the mouse conditions to the pairing of the tone and shock, it may exhibit a freezing behavior due to the fear that the mild foot shock imparts to the mouse. Freezing behavior on the test day suggests that the mouse has learned that it received a shock in this particular context when the white noise is turned off. This test is considered to provide data about emotional-based learning and memory.

Aggression and other social behaviors can be monitored by observation or quantification of behaviors such as grooming, home cage behaviors (e.g., nesting, huddling, playing, and barbering) isolation-induced fighting, maternal behavior, parental behavior, social interaction, social investigation. Particular tests include the Partition test, the social defeat test, the Resident versus Intruder test, and the Social Place Preference test. Any of the foregoing can be used to determine a mouse's susceptibility to acute or chronic administration of pharmacological agents. The resident-intruder paradigm is an assay that demonstrates species-specific aggressive behavior. This test is conducted by individually housing an animal (the resident) and introducing a new animal of the same gender (the intruder) into the cage. The new animal is viewed by the resident animal as an intruder and displays aggressive behaviors toward the intruder (Crusio, *Behav. Genet.* 26:459-533, 1996). The normal display of aggression towards an intruder may serve as a model for examining increased or decreased aggression to a normal environmental situation.

One test for social dominance can be carried out to assay social interactions and social behaviors. In the so-called "tube test," a mouse is placed into the end of a plexiglass cylinder and another mouse (called a social cohort) is placed at the other end of the tube. The animal that backs out of the tube first is considered the loser and the mouse that

5 remains in the tube is considered the winner. In general, an animal that backs out of the tube during the first round generally backs out of the tube in subsequent rounds. A ranking can then be given to each animal, thus identifying the dominance or submissive status of an animal within a social context, as well as detecting abnormal social behaviors that can be related to antisocial personality conditions or disorders.

10 Behaviors relating to reward and addiction are assessed using tests that measure, for example, reward and place preference, self-administration of drugs of abuse (acute and chronic), sensitization and tolerance to drugs of abuse, sensitization to the motor activating properties of drugs, tolerance to repeated analgesic drug administration, or withdrawal symptoms after repeated self-administration of drugs of abuse. The impact on self-

15 administration of drugs of abuse in stress tests can also be used to assess addiction.

Tolerance and sensitivity to ethanol and cocaine can be tested, for example, by examining core body temperature of the mice after an intra-peritoneal (i.p) injection of cocaine or ethanol. Initial sensitivity to cocaine and alcohol can be measured in mice after a single (acute) dose. In rodents, repeated exposure to alcohol or cocaine via repeated

20 injections across days has been shown to produce tolerance. In both the alcohol studies and the cocaine studies, mice are administered an i.p. dose, and core body temperature is measured post injection with a digital thermometer with a rectal probe. On Day 2, mice are administered the same dose using the same route, and temperature again recorded post injection. For the cocaine studies, mice will be administered an i.p. dose and core body

25 temperature will be measured post injection with a rectal thermometer. On Day 2 mice will be administered the same dose using the same route and temperature will be recorded post injection. Tolerance to the drug is indicated by an increase in body temperature on the second day of drug administration compared to the first day of drug administration. These assays detect sensitivity to various drug substances and, thus, are indicators of alcohol or

30 cocaine use disorders.

The rewarding effects of various substances of abuse can be studied using the conditioned place preference paradigm and self-administration tests. The place preference paradigm is a non-invasive method that is amenable to classical Pavlovian conditioning. The rewarding drug serves as an unconditioned stimulus (US) that is paired with an environment that serves as the conditioned stimulus (CS). Given a choice between exploring a novel environment and the drug-paired CS environment, the animals prefer the drug-paired CS environment, thereby demonstrating conditioned place preference (Itzhak and Martin, *Neuropsychopharmacol.* 26:130-134, 2002). This Pavlovian conditioned response to a drug of abuse has been postulated to be involved in drug-seeking behavior and relapse following exposure to cues that were previously associated with drug use. Self-administration studies, in general, allow the animal to regulate the administration of a drug to its nervous system. With these types of studies, extinction and reinstatement of drug intake behaviors can be examined and may serve as a model for drug-seeking behavior and relapse in humans (Stewart et al., *Brain Res.* 457:287-294, 1988).

Administration of a drug such as bicuculine can be utilized to study an animal's susceptibility to seizures or seizure-like events. Mice that enter into classical seizure symptoms earliest are considered to be more susceptible to seizures. Likewise, mice that present seizure symptoms later than normal, are considered to be more resistant to seizures. This assay may allow the identification of alterations central to the formation of seizure disorders and related conditions.

Methods for performing many of the foregoing screens are well known in the art (see, e.g., Brunner et al., *J. Exp. Psychol. Anim. Behav. Process* 20:331-346, 1994; Crawley, *What's Wrong With My Mouse?* (John Wiley and Sons, Somerset, NJ, 2000); Crawley et al., (eds.); *Current Protocols in Neuroscience* (John Wiley and Sons, Somerset, NJ, 2001); Crawley et al., *Hormones Behav.* 31:197-211, 1997; Crawley et al., *Psychopharmacol. (Berl)* 132:107-124, 1997; Galey et al., *Neurosci. Lett.* 143:87-90, 1992; Hascoet et al., *Pharmacol. Biochem. Behav.* 65:339-344, 2000; Martinez-Mota et al., *Psychoneuroendocrinol.* 25:109-120, 2000; Mogil et al., *Pain* 80: 67-82, 1999; Toubas et al., *Pharmacol. Biochem. Behav.* 35:121-126, 1990; Van Der Hyden et al., *Physiol. Behav.* 62:463-470, 1997; Walker et al., *Molec. Med. Today* 5:319-321, 1999).

In addition to the initial screening of test compounds, the animals having mutant GPCR genes are useful for further testing of efficacy and safety of drugs or agents first identified using one of the other screening methods described herein. Cells taken from the animal and placed in culture can also be exposed to test compounds.

5

Testing mice for other diseases, disorders, conditions, or syndromes

The effect of overexpression, underexpression, misexpression, or mutation of a GPCR of the present invention can be assayed, for example, using any of a wide variety of measurements or tests; Barbee et al., *Am. J. Physiol.* 263:R728-733, 1992; Berul et al., *Circulation* 94:2641-2648, 1996; Butz et al., *Physiol. Genomics* 5:89-97, 2001; Coatney, *Ilar J.* 42:233-247, 2001; Crawley et al., *Horm. Behav.* 31:197-211, 1997; Crawley et al., *Psychopharmacol. (Berl)* 132:107-124, 1997; Crawley et al. (eds.) *Current Protocols in Neuroscience* (John Wiley and Sons, 2001); Furukawa et al., *Lab. Anim. Sci.* 48:357-363, 1998; Hartley et al., *Ilar J.* 43:147-158, 2002; Kregge et al., *Hypertension* 25:1111-1115, 1995; Kurien et al., *Lab. Anim.* 33:83-86, 1999; Lorenz et al., *Am. J. Physiol.* 272:H1137-H1146, 1997; Mattson, *Am. J. Physiol.* 274:R564-R570, 1998; Mitchell et al., *Am. J. Physiol.* 274:H747-H751, 1998; Pollick et al., *J. Am. Soc. Echocardiogr.* 8:602-610, 1995; Rogers et al., *Mamm. Genome* 8:711-713, 1997; Rogers et al., *Neurosci. Lett.* 306:89-92, 2001; Shih et al., *Nat. Med.* 6:711-714, 2000; Wiesmann et al., *Magma* 6:186-188, 1998; Irwin, *Psychopharmacologia* 13:222-257, 1968; Brayton et al., *Vet. Pathol.* 38:1-19, 2001; Ward et al., *Pathology of Genetically Engineered Mice* (Iowa State University Press, Ames, Iowa, 2000).

General physiological tests and measurements include, for example, measurement of body temperature, body length and proportions, body mass index, general health appearance, vocalization during handling, lacrimation and salivation, visual tests (e.g., visual cliff, reaching response, visual menace), auditory tests (e.g., click test, acoustic startle, acoustic threshold), olfactory tests (e.g., sniffing and habituation to a novel odor, finding buried food), reflex tests (e.g., righting reflex, eye blink, whisker twitch), measurement of metabolic hormones (e.g., leptin, IGF-1, insulin, metabolites), whole body densitometry by dual energy x-ray absorptometry DEXA or high resolution radiography

(Faxitron), and necropsy examination of organ systems.

Identification of a skin disease or disorder may be made by histopathology, examination of fur and skin condition, examination of pigmentation of fur and skin, and determination of wound healing by an ear punch test.

- 5 Cardiac diseases and disorders can be identified, for example, by means of histopathology or electrocardiography, or by determination of blood pressure, blood velocity, blood flow, or pulse rate.

- 10 Identifying mice having a disorder of the respiratory system, including the lungs, nose, larynx, trachea, and pleura, can be performed by histopathology, or by determination of lung capacity, respiration rate, VO_2 , pCO_2 , arterial pO_2 , and tidal volume.

- 15 Testing mice for disorders of the immune and hematopoietic systems, including blood, bone marrow, thymus, spleen and lymph nodes, can be performed, for example, by histopathology, delayed hypersensitivity test, measurement of serum immunoglobins, blood pH, or coagulation time, volumetric analysis using Evans blue dye technique, or analysis of bone marrow smears, hematocrit, hemoglobin, erythrocytes, reticulocytes, leukocytes, platelets, prothrombin, electrolytes, or lymphocytes.

- 20 Knock-out or transgenic mice of the present invention may have a disease or disorder of the digestive tract (e.g., the esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, and rectum). Testing for these diseases and disorders of the digestive tract, may include fecal analysis, measurement of digestive enzymes, or histopathology.

Identification of mice having a disease or disorder of the liver may be by means of histopathology or analysis of total proteins, albumin, bilirubin, creatinine, transaminase, cholesterol, aldolase, ammonia, sorbitol dehydrogenase, or serum bile acids

- 25 Testing for disorders of the pancreas in mice may be performed, for example, by histopathology, a glucose tolerance test, an insulin challenge test, or analysis of glucose, insulin, glucagon, or exocrine enzymes.

- 30 Testing for diseases or disorders of the urinary system, including the kidney, ureter, and urinary bladder, may include histopathological examination, or analysis of sodium osmolality, potassium, urea nitrates, creatinine, chloride, bicarbonate, glucose, cystatin c, or urine electrolytes or blood pressure.

Testing mice for diseases or disorders of the female reproductive tract, including the ovary, oviducts, uterus, and vagina, may include determination of fertility (e.g., by vaginal plugging), cyclicity (e.g., by vaginal smears), parturition (e.g., by litter size), maternal behavior (e.g., by pup survival and nesting, histopathology, or analysis of levels of
5 estrogens, follicle-stimulating hormone, or luteinizing hormone). Similarly, testing mice for diseases or disorders of the male reproductive tract, including the testis, epididymus, prostate, seminal glands, accessory glands, and penis may include histopathological examination, determination of fertility, sperm counts and motility, erectile capacity (e.g., by plethysmography), and/or analysis of levels of androgens, follicle-stimulating hormone,
10 PSA or luteinizing hormone.

Mice having diseases or disorders of the musculature may be identified by histopathology, electromyography, testing of muscle strength and contractibility, or analysis of levels of creatinine, lactate, myoglobin, or isoenzymes.

Testing mice for diseases or disorders of the skeletal system may include, for
15 example, bone strength determination, histopathological examination, mineral analysis, dual energy x-ray absorptiometry (DEXA), or analysis of osteocalcin, calcitrol, urine pyridinium, or N-telopeptide.

Testing mice for diseases or disorders of the endocrine system, including the pituitary, thyroid gland, adrenal gland, and mammary glands, may also be performed.
20 Testing may include, for example, histopathological examination, determination of lactation capacity, testing of hormone release, and/or analysis of corticosterone, adrenocorticotrophic hormone, corticotrophin releasing hormone, thyroid hormone, thyrotropin releasing hormone, thyroid stimulating hormone, chorionic gonadotropin, growth type hormone, growth type hormone-releasing hormone, somatostatin, prolactin, alpha-melanocyte
25 stimulating hormone, follicle-stimulating hormone, luteinizing hormone, or gonadotropin hormone-releasing hormone.

Finally, testing for mice for diseases or disorders of the nervous system, including the brain, spinal cord and peripheral ganglia, may include determination of stroke susceptibility (e.g., by focal ischemia or cerebral occlusion), histopathological examination,
30 determination of neurotransmitter release (e.g., by microdialysis or cell culture) or synaptic

transmission (e.g., by electrophysiology in brain slices), brain wave analysis by electroencephalography (EEG), whole brain imaging by magnetic resonance imaging, transmitter content determination by HPLC, protein localization and cell type analysis (e.g., by immunohistochemistry), neuron apoptosis determination (e.g., by TUNEL assay), total
5 cell count, or examination of fiber tract localization and integrity, dendritic and axonal morphology, and structural integrity by morphometric analysis.

GPR85 Knock out Mice

Methods

10 Home cage activity was monitored by a photobeam system (Accuscan Instruments) that is exterior to the cage. The photobeams provide information of when an animal is moving around in its home cage. Animals in their home cage were placed in the photobeam boxes and tested for activity over a three day period. This data will give us insight into the animal's circadian rhythms of activity. Measurements examined include activity onset,
15 average day activity, average night activity, and average activity over a 24 hour period. Food consumption was also measured during this same time frame (Test Days 1-3). The amount of food placed in the cage was measured before Test Day 1 and at the end of Test Day 3, and the average over the 3 days will give information on the amount of food eaten in a 24 hour period.

20 Open field activity was monitored in open field chambers (Accuscan Instruments) measuring 40 cm x 40 cm x 40 cm. Locomotor activity is detected by photobeams breaks as the animal crosses each beam. Measurements used to assess locomotor activity includes: Horizontal activity (total distance traveled in centimeters (cm)), total number of rearing events (animal raises up on hindlimbs), and distance traveled in the center compared to total
25 distance traveled (center:total distance ratio). Mice are placed in the center of the field and then left undisturbed for 20 minutes in order to measure spontaneous activity in a novel environment. Mice will normally explore the edges/walls first and over time spend more time in the center as they become familiar with the environment. This assay gives us data on the general activity level of mice (i.e. hypo- or hyper-active).

30 The hot plate test for nociception (pain) was carried out by placing a mouse on a 55°

C hot plate (Accuscan Instruments) inside a 15 cm x 15 cm enclosure (to restrict them from walking off the hot plate). The latency to a hind limb response (shake or lick) is measured with a maximum cut-off time of 30 seconds to ensure that tissue damage does not occur. The test is performed once for each mouse. This assay gives data on the animal's general
5 nociceptive response.

The light-dark exploration test measures the conflict between the natural tendencies of mice to explore a novel environment but to avoid the aversive properties of a brightly lit (anxiety-provoking) open area. The brightly lit compartment (27 cm x 20 cm x 30 cm) comprises two-thirds of the surface area while the dark compartment (18 cm x 20 cm x 30
10 cm) comprises one-third of the surface area. An opening is designed to allow the mouse access to both compartments.

The stress-induced hyperthermia test measures anticipatory anxiety and reflects an unconditioned physiological response where the rectal temperature of a mouse increases in response to the stressor of handling and rectal temperature measurement. The change in
15 temperature from baseline (first) recording to the second temperature recording is a demonstration of the degree of stress/anxiety of that animal.

The basal temperature (T_0) of mice is measured rectally (Physitemp). A few seconds later the mouse was placed in the light-dark box for 6 minutes. Immediately after the completion of the light-dark box test, the mouse is removed from the box and the
20 stressed temperature (T_1) was determined. Measurements used to assess anxiety-related responses are the total number of transitions in the light-dark box and the change in body temp ($T_1 - T_0$) from baseline over the 6 minute test.

The tail suspension assay involves the use of an automated tail suspension apparatus (Med Associates) where the animal is suspended by its tail on a metal plate that is
25 connected to a load cell amplifier. The load cell amplifier picks up the animal's movements (struggle to escape) and this data is collected by a computer during the 6 minute test session. The time spent struggling is a measure of learned helplessness behavior or behavioral despair, and the latency to the onset of the end of the struggling can be increased by clinically effective antidepressants. The time the animal spends immobile is the measure
30 used to assess the depressive-like response of the animal.

The tube test for social dominance is carried out to assay social interactions and social behaviors. An experimental mouse is placed into the end of a PVC cylinder (6 cm in diameter, 30 cm in length) and another mouse (called a social cohort) is placed at the other end of the tube. The animal that backs out of the tube first is considered the loser and the mouse that remains in the tube is considered the winner. In general, an animal that backs out of the tube first round is considered to be socially submissive while an animal that causes another animal to back out is considered to be socially dominant. The percentage of winners and losers can then be measured to determine if a group of animals is socially dominant or submissive.

Prepulse inhibition of the acoustic startle response (PPI) was tested using the SR-Lab System (San Diego Instruments). A test session began by placing a mouse in the Plexiglas cylinder where it was left undisturbed for 3 minutes. A test session consisted of six different trial types. One trial type was a 40 ms, 120 dB sound burst used as the startle stimulus. There were four different acoustic prepulse plus acoustic startle stimulus trials. The prepulse sound was presented 100 ms before the startle stimulus. The 20 ms prepulse sounds were 73, 76, 79, and 82 dB. Finally, there were 70 dB trials where no stimulus was presented to measure baseline movement in the cylinders. Six blocks of the six trial types were presented in pseudorandom order such that each trial type was presented once within a block of six trials. The average intertribal interval was 15 seconds, with a range of 10-20 seconds. The startle response was recorded for 65 ms (measuring the response every 1 ms) starting with the onset of the startle stimulus. The background noise level in each chamber was 70 dB. The maximum startle amplitude recorded during the 65 ms sampling window was used as the dependent variable. Animals that did not demonstrate maximum startle amplitude greater than 100 were excluded from analyses. Measurements used to assess PPI are the maximum startle amplitude and the percent each of the 4 prepulses inhibits the startle response.

Context and auditory cue fear conditioning requires a training and testing day. Conditioned fear involves placing a mouse in an enclosed chamber measuring 30 cm x 24 cm x 24 cm. The floor of the chamber is made up of metal rods equipped to deliver a mild electrical shock (the unconditioned stimulus, 0.5 mA, 2 sec) to the mouse's feet. Electrical

shock is paired with a tone such that the shock is delivered immediately when the tone turns off. The training day consists of placing the mouse in the chamber and allowing it to explore the environment for 2 minutes. At the end of 2 minutes a 75-80 dB white noise is turned on (the conditioning stimulus, CS) for 30 seconds. A 2 second, 0.5 mA footshock is paired
5 with the white noise turning off. This training trial is then repeated again. The experiment takes approximately 5 minutes on the training day. The mouse is tested 24 hours later by separately assaying the amount of freezing it shows in the context (Context Test) in which it was shocked and the amount of freezing it shows to the tone (CS Test). Freezing behavior on the test days suggests that the mouse has learned that it received a shock in this particular
10 context and when the white noise is turned off. This test measures emotional-based learning and memory.

Tolerance and sensitivity to ethyl alcohol (ethanol) will be tested by examining core body temperature of the mice before and after an intra-peritoneal (i.p) injection of ethanol. Initial sensitivity to alcohol is measured in mice after a single (acute) dose. In rodents
15 repeated exposure to alcohol via repeated injections across days has been shown to produce tolerance. Core body temperature was measured rectally (T_0) (Physitemp) and then the mice were administered an i.p. dose of 2.5 mg/kg and placed in a Plexiglas dosing chamber that is the same size as the animal's cage. Core body temperature was measured rectally 30 minutes post injection (T_1) and returned to their home cage. Mice were housed in the
20 testing room overnight. On the next day mice were treated identically as the previous day, with a 30 minute interval between ethanol administration and T_1 . Sensitivity to ethanol is measured by calculating the difference in body temp ($T_1 - T_0$) while tolerance is measured by calculating the difference between the temperature changes for each day.

For cocaine studies, mice were administered an i.p. dose of 40 mg/kg and
25 immediately placed into the open field arenas (see description above) to assess locomotor activity for 20 minutes post injection. The next day mice were administered the same dose using the same route, and locomotor activity measured in the open field arenas for 20 minutes post injection. Initial sensitivity to the stimulant effects of cocaine are seen as an increase in locomotor activity.

30

RESULTS

Data Analysis

Data analysis for the various behavioral paradigms were analyzed using two-way (genotype x gender) or three-way (genotype x gender x repeated measure such as time) analysis of variance (ANOVA). Tube test analysis was carried out using the Mann-Whitney U test for nonparametric analysis. Significance was set at $P < 0.100$. If a score of $P < 0.100$ was obtained for a test in the Primary Screen, an additional set of wild-type and knockout mice were obtained to repeat the tests which showed a significant finding.

10 Mice

For tests where the P value met our criteria for statistical significance ($P < 0.100$), an additional set of wild-type and knockout mice were used to test if the initial findings could be replicated. The mice were housed in a room with a 12:12h light:dark schedule with access to food and water *ad libitum*. Mice began testing at 10-12 weeks of age.

15 **Home Cage Activity.** A significant, replicable Gender X Genotype interaction was observed for total activity levels between KO and WT mice. As shown in Figure 6, post-hoc analysis indicates that KO females are more active at night compared with WT females ($F_{(1,41)} = 6.61$, $P = .014$) while activity levels during the day are equal. There was no significant difference between WT and KO male mice for total activity levels. There was also no significant difference between WT and KO mice for time of activity onset. These results suggest that GPR85 may be involved with basal nighttime activity, which may impact circadian rhythms and sleep patterns.

25 **Stress-Induced Hyperthermia (SIH).** The Light Dark Exploration test (LD) and SIH was combined into a single paradigm as described above. The number of transitions between the light and dark portions of the box during the LD test was not different between genotypes. However, a significant, replicable genotype effect was observed in the SIH test for the change in temperature ($T_0 - T_1$), which is determined by subtracting the baseline temperature (T_0) from the temperature measurement 6 minutes later (T_1), at the end of the Light-Dark test. As shown in Figure 7, KO mice demonstrate an increased change in temperature compared to the WT mice ($F_{(1,49)} = 3.195$, $P = .080$), suggesting an increased

30

stress/anxiety response. This result suggests that GPR85 is involved in stress and/or anxiety.

A significant difference was also noted for basal temperatures between WT and KO mice ($F_{(1,49)} = 15.832$, $P = < .001$), with KO mice consistently demonstrating a decreased
5 core body temperature compared to WT litter mates. This suggests that GPR85 has a role in thermoregulation.

Context Fear Conditioning. The conditioned fear paradigm is used to assay a fear-based response using a Pavlovian learning and memory paradigm. A significant, replicable genotype effect was demonstrated in the Context Fear paradigm for the levels of freezing to
10 the environment in which the animals had received a mild footshock paired with an auditory cue. As shown in Figure 8, the GPR85 KO mice displayed significantly more freezing responses than the WT mice ($F_{(1,43)} = 6.898$, $P = .012$). These findings indicate GPR85 KO mice have an enhanced learning and memory response to fear conditioning that is associated with the context or environment where the shock occurred.

Ethanol Sensitivity and Tolerance. This two day paradigm is used to assay the
15 acute response to the hypothermic/sedative effects of ethanol by measuring the difference in core body temperature before and after administration of a 2.5 g/kg i.p. injection of ethanol. Repeated injections of ethanol over days in rodents have been shown to produce tolerance in as few as 2 days. As shown in Figure 9, i.p. injections of ethanol reduced body
20 temperature in both WT and KO mice. The results of this paradigm also show that the GPR85 KO mice exhibit reduced initial sensitivity and normal tolerance to the hypothermic effects of ethanol when compared to WT mice ($F_{(1,49)} = 17.485$, $P = < .001$). These results indicate GPR85 is involved in regulating the behavioral responses effects of ethanol and possibly other drugs of abuse.

GPR85 KO mice demonstrated a decrease in their sensitivity to ethanol upon a
25 second, independent exposure to ethanol. A total of 16 (8 KO and 8 WT) mice were dosed with ethanol, using the same dose and route of administration previously used, and 4 of the 8 KO mice were noticeable less sedated when compared with other mice that received the same dose. This result further demonstrates that GPR85 KO mice are less sensitive to the
30 effects of ethanol.

Weight measurements. Weight measurements were taken (Table 34). The weight data indicates that the male KO mice weigh approximately 15% less than WT mice suggesting that this gene may be involved in metabolism and other processes that influence weight gain/loss.

Table 34. Weight data. The number of mice per WT and KO group is shown above and below the value respectively.

GPR85 MALES

| | | 10 WKS | 11 WKS | 12 WKS | 13 WKS | 14 WKS |
|------|------|--------|--------|--------|--------|--------|
| | | n = 4 | n = 7 | n = 12 | n = 4 | n = 2 |
| MEAN | WT M | 26.0 | 24.9 | 26.1 | 25.1 | 26.3 |
| MEAN | KO M | | 20.1 | 22.7 | 22.3 | 22.4 |
| | | n = 0 | n = 2 | n = 12 | n = 8 | n = 7 |

10

Summary. In summary, GPR85 mice demonstrated several behavioral differences when compared to their WT littermates. GPR85 females demonstrated an increase in basal nighttime activity compared to WT females. This result indicates GPR85 is involved in the modulation of activity and activity patterns. GPR85 KO male mice weighed less than their WT littermates, suggesting that this gene may be involved in metabolism and other processes that influence weight gain/loss. GPR85 KO mice also demonstrated an increased stress/anxiety response, impaired thermoregulation, enhanced learning and memory, and decreased sensitivity to a drug of abuse. These results suggest that this gene is involved in the following conditions and disorders: thermoregulatory dysfunction, metabolism disorders, obesity, diabetes, activity disorders (including but not limited to ADD and ADHD) circadian rhythm disorders, and sleep disorders, learning and memory processes (including but not limited to dementia and Alzheimer's disease), anxiety disorders, stress disorders, and addiction.

25 Therapy

Compounds of the invention, including but not limited to, GPCR polypeptides, GPCR polynucleotides, and any therapeutic agent that modulates biological activity or

expression of a GPCR polypeptide identified using any of the methods disclosed herein, may be administered with a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer such compositions to patients. Any appropriate route of administration may be employed, for example, parenteral, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, or oral administration. Therapeutic formulations may be in the form of liquid solutions or suspension; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

Methods well known in the art for making formulations are found in, for example, Remington: The Science and Practice of Pharmacy, (20th ed.) ed. A.R. Gennaro AR., 2000, Lippincott: Philadelphia. Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated naphthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for agonists of the invention include ethylenevinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents

for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

5 Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor ELTM (BASF, Parsippany, NJ) or phosphate buffered saline (PBS).

10 In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, 15 for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such 20 as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

 Sterile injectable solutions can be prepared by incorporating the active compound in 25 the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred 30 methods of preparation are vacuum drying and freeze-drying which yields a powder of the

active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral
5 therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The
10 tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring
15 agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For
20 transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are
25 formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery. In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a
30 controlled release formulation, including implants and microencapsulated delivery systems.

Biodegradable, biocompatible polymers can be used, such as ethylene-vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.

Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova
5 Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages
10 for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Depending on the type and severity of the disease, about 1 ug/kg to 15 mg/kg (e.g., 0.1 to 20 mg/kg) of antibody is an initial candidate dosage for administration to the patient, whether, for example, by one or more separate
15 administrations, or by continuous infusion. A typical daily dosage might range from about 1 Rtg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful. The progress of this therapy can be monitored by standard
20 techniques and assays. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

Toxicity and therapeutic efficacy of such compounds can be determined by standard
25 pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side
30 effects may be used, care should be taken to design a delivery system that targets such

compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

The skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

The present invention encompasses agents that modulate expression or activity. An agent may, for example, be a small molecule. For example, such small molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs, organic or inorganic compounds (i.e., including heteroorganic and organometallic compounds) having a molecular weight less than about 10,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 5,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 1,000 grams per mole, organic or inorganic compounds having a molecular weight less than about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such compounds. It is understood that appropriate doses of small molecule agents depends upon a number of

factors within the ken of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of the small molecule will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner
5 desires the small molecule to have upon the nucleic acid or polypeptide of the invention.

It is understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (e.g., a human) in order to
10 modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific compound employed, the age,
15 body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.]

Diagnostics

20 Expression, biological activity, and mutational analysis of a GPCR gene of the invention can each serve as a diagnostic tool for a disease or disorder involving the GPCR; thus determination of the genetic subtyping of a GPCR gene sequence can be used to subtype individuals or families to determine their predisposition for developing a particular disease or disorder.

25 An exemplary method for detecting the presence or absence of a GPCR protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of detecting GPCR protein or nucleic acid (e.g., mRNA, genomic DNA) that encodes GPCR protein such that the presence of GPCR protein or nucleic acid is detected in the biological
30 sample. A preferred agent for detecting GPCR mRNA or genomic DNA is a labeled nucleic

acid probe capable of hybridizing to GPCR mRNA or genomic DNA.

The nucleic acid probe can be, for example, a full-length GPCR nucleic acid, such as the nucleic acid of Table 1, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under
5 stringent conditions to GPCR mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

Another method for detecting the presence or absence of a GPCR protein in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with an antibody that is capable of detecting GPCR protein. Where
10 said antibody capable of binding to the GPCR protein preferably has a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (e.g., Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as
15 indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as
20 tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect GPCR mRNA, protein, or genomic DNA in a biological sample in vitro as well as in vivo. For example, in vitro techniques for detection of GPCR mRNA include Northern hybridizations and in situ hybridizations. In vitro techniques for detection of GPCR protein include enzyme linked immunosorbent assays (ELISAs),
25 Western blots, immunoprecipitations and immunofluorescence. In vitro techniques for detection of GPCR genomic DNA include Southern hybridizations. Furthermore, in vivo techniques for detection of GPCR protein include introducing into a subject a labeled anti-GPCR antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a serum sample isolated by conventional means from a subject.

5 In another embodiment, the methods further involve obtaining a control biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting GPCR protein, mRNA, or genomic DNA, such that the presence of GPCR protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of GPCR protein, mRNA or genomic DNA in the control sample
10 with the presence of GPCR protein, mRNA or genomic DNA in the test sample.

The invention also encompasses kits for detecting the presence of GPCR in a biological sample. For example, the kit can comprise a labeled compound or agent capable of detecting GPCR protein or mRNA in a biological sample; means for determining the amount of GPCR in the sample; and means for comparing the amount of GPCR in the
15 sample with a standard. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect GPCR protein or nucleic acid.

The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant GPCR
20 expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with a misregulation in GPCR protein activity or nucleic acid expression, such as a weight, cardiovascular, neurological or endocrine disorder. Alternatively, the prognostic assays can be utilized to identify a subject having or
25 at risk for developing a disorder associated with a misregulation in GPCR protein activity or nucleic acid expression, such as a weight, cardiovascular, neural or endocrine disorder. Thus, the present invention provides a method for identifying a disease or disorder associated with aberrant GPCR expression or activity in which a test sample is obtained from a subject and GPCR protein or nucleic acid (e.g., mRNA or genomic DNA) is
30 detected, wherein the presence of GPCR protein or nucleic acid is diagnostic for a subject

having or at risk of developing a disease or disorder associated with aberrant GPCR expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of interest. For example, a test sample can be a biological fluid (e.g., serum), cell sample, or tissue.

5 Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (e.g., an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant GPCR expression or activity. For example, such methods can be used to determine whether a subject can be effectively
10 treated with an agent for a weight, cardiovascular, neural or endocrine disorder. Thus, the present invention provides methods for determining whether a subject can be effectively treated with an agent for a disorder associated with aberrant GPCR expression or activity in which a test sample is obtained and GPCR protein or nucleic acid expression or activity is detected (e.g., wherein the abundance of GPCR protein or nucleic acid expression or
15 activity is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant LGR6 expression or activity).

 The methods of the invention can also be used to detect genetic alterations in a GPCR gene, thereby determining if a subject with the altered gene is at risk for a disorder characterized by misregulation in GPCR protein activity or nucleic acid expression, such as
20 a weight, cardiovascular, neural or endocrine disorder. In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a genetic alteration characterized by at least one of an alteration affecting the integrity of a gene encoding a GPCR-protein, or the mis- expression of the GPCR gene. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a
25 deletion of one or more nucleotides from a GPCR gene; 2) an addition of one or more nucleotides to a GPCR gene; 3) a substitution of one or more nucleotides of a GPCR gene, 4) a chromosomal rearrangement of a GPCR gene; 5) an alteration in the level of a messenger RNA transcript of a GPCR gene, 6) aberrant modification of a GPCR gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type
30 splicing pattern of a messenger RNA transcript of a GPCR gene, 8) a non-wild type level of

a GPCR -protein, 9) allelic loss of a GPCR gene, and 10) inappropriate post-translational modification of an GPCR - protein. As described herein, there are a large number of assays known in the art which can be used for detecting alterations in a GPCR gene. A preferred biological sample is a tissue or serum sample isolated by conventional means from a
5 subject.

In certain embodiments, detection of the alteration involves the use of a probe/primer in a polymerase chain reaction (PCR) such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran et al. (1988) Science 241:1077-1080; and Nakazawa et al. (1994) Proc. Natl. Acad Sci. USA 91:360-364), the
10 latter of which can be particularly useful for detecting point mutations in the GPCR - gene (see Abravaya et al. (1995) Nucleic Acids Res.23:675-682). This method can include the steps of collecting a sample of cells from a subject, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a GPCR gene under conditions such that
15 hybridization and amplification of the LGR6-gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. et al., (1990) Proc. Natl. Acad Sci. USA 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. et al., (1989) Proc. Nail. Acad Sci. USA 86:1173- 1177), Q-Beta Replicase (Lizardi, P.M. et al. (1988) Bio-Technology 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using
25 techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers.

In an alternative embodiment, mutations in a GPCR gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and
30 control DNA is isolated, amplified (optionally), digested with one or more restriction

endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence specific ribozymes can be used to score for the presence of specific mutations by development or loss of a ribozyme
5 cleavage site.

In other embodiments, genetic mutations in GPCR can be identified by hybridizing a sample and control nucleic acids, e.g., DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotides probes (Cronin, M.T. et al. (1996) Human Mutation 7: 244-255; Kozal, M.J. et al. (1996) Nature Medicine 2: 753- 759). For example,
10 genetic mutations in GPCR can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. et al. (1996) Human Mutation 7: 244-255.

Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences
15 by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary
20 to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the GPCR gene and detect mutations by comparing the sequence of the sample LGR6 with the corresponding wild- type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam
25 and Gilbert (1977) Proc. Nati. Acad. Sci. USA 74:560 or Sanger (1977) Proc. Nati. Acad. Sci. USA 74:5463. It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the diagnostic assays ((1995) Biotechniques 19:448), including sequencing by mass spectrometry (Cohen et al. (1996) Adv. Chromatogr. 36:127-162; and Griffin et al. (1993) AppL. Biochem. Biotechnol. 38:147-159).

Other methods for detecting mutations in the GPCR gene include methods in which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers et al. (1985) Science 230:1242). In general, the technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type GPCR sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent that cleaves single-stranded regions of the duplex such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with SI nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. For examples see, Cotton et al. (1988) Proc. Natl Acad Sci USA 85:4397; and Saleeba et al. (1992) Methods Enzymol. 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.

In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in GPCR cDNAs obtained from samples of cells. For example, the mutY enzyme of E. coli cleaves A at G/A mismatches and the thymidine DNA glycosylase from HeLa cells cleaves T at G/T mismatches (Hsu et al. (1994) Carcinogenesis 15:1657-1662). According to an exemplary embodiment, a probe based on a GPCR sequence, e.g., a wild-type GPCR sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the like.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in GPCR genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type

nucleic acids (Orita et al. (1989) *Proc Natl. Acad. Sci USA*: 86:2766, see also Cotton (1993) *Mutat. Res.* 285:125-144; and Hayashi (1992) *Genet. Anal. Tech. AppL.* 9:73-79). Single-stranded DNA fragments of sample and control LGR6 nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies
5 according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change.

The DNA fragments may be labeled or detected with labeled probes. The sensitivity of the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject
10 method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (Keen et al. (1991) *Trends Genet* 7:5).

In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (Myers et al. (1985) *Nature* 313:495). When DGGE is
15 used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (Rosenbaum and Reissner (1987) *Biophys Chem* 265:12753).

20 Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (Saiki et al. (1986) *Nature*
25 324:163); Saiki et al. (1989) *Proc. Natl Acad Sci USA* 86:6230). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA. Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant
30 invention.

Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs et al. (1989) *Nucleic Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce
5 polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini et al. (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad Sci USA* 88:189). In such cases, ligation will occur only if
10 there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent
15 described herein, which may be conveniently used, e.g., in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a GPCR gene.

This diagnostic process can also lead to the tailoring of drug treatments according to patient genotype, including prediction of side effects upon administration of drugs (referred
20 to herein as pharmacogenomics). Pharmacogenomics allows for the selection of agents (e.g., drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (e.g., the genotype of the individual is examined to determine the ability of the individual to respond to a particular agent).

Agents, or modulators, that have a stimulatory or inhibitory effect on the biological
25 activity or gene expression of a GPCR polypeptide of the invention can be administered to individuals to treat disorders associated with aberrant GPCR activity. In conjunction with such treatment, the pharmacogenomics (i.e., the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of the individual may be considered. Differences in efficacy of therapeutics can lead to severe
30 toxicity or therapeutic failure by altering the relation between dose and blood concentration

of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (e.g., drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens.

- 5 Accordingly, the activity of a GPCR polypeptide of the invention, expression of a GPCR nucleic acid, or polymorphic content of GPCR genes in an individual can be determined to select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs because of altered drug disposition and abnormal action in affected
10 persons (Eichelbaum, Clin. Exp. Pharmacol. Physiol., 23:983-985, 1996; Linder, Clin. Chem., 43:254-266, 1997). In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). Altered drug action may occur in
15 a patient having a polymorphism (e.g., an single nucleotide polymorphism or SNP) in promoter, intronic, or exonic sequences of a GPCR polypeptide of the invention. Thus, determining the presence and prevalence of polymorphisms may allow for prediction of a patient's response to a particular therapeutic agent. In particular, polymorphisms in the promoter region may be critical in determining the risk that a patient will develop a
20 particular disease or disorder.

Gene Therapy

Gene therapy is another potential therapeutic approach in which normal copies of a gene or nucleic acid encoding sense RNA for a GPCR of the invention are introduced into
25 cells to successfully produce GPCR polypeptide. The gene must be delivered to those cells in a form in which it can be taken up and encode for sufficient protein to provide effective function. Alternatively, GPCR antisense RNA and DNA or other interfering RNAs (RNAi), such as siRNAs, or a gene that expresses such RNA may be introduced into cells that express, perhaps excessively, a wild-type or polymorphic GPCR polypeptide. The gene or
30 RNA must be delivered to those cells in a form in which it can be taken up and provide for

sufficient RNA to provide effective function.

Retroviral vectors, adenoviral vectors, adenovirus-associated viral vectors, or other viral vectors with the appropriate tropism for a particular cell involved in disease may be used as a gene transfer delivery system for delivering such polynucleotides. Numerous
5 vectors useful for this purpose are generally known (Friedman, Science 244:1275-1281, 1989; Eglitis et al., BioTechniques 6:608-614, 1988; Tolstoshev et al., Curr. Opin. Biotech. 1:55-61, 1990; Sharp, Lancet 337:1277-1278, 1991; Cornetta et al., Nucl. Acid Res. Mol. Biol. 36:311-322, 1987; Anderson, Science 226:401-409, 1984; Moen, Blood Cells 17:407-416, 1991; Miller et al., Biotech. 7:980-990, 1989; Le Gal La Salle et al., Science 259:988-
10 990, 1993; Johnson, Chest 107:77S-83S, 1995). Retroviral vectors are particularly well developed and have been used in clinical settings (Rosenberg et al., N. Engl. J. Med. 323:370, 1990; Anderson et al., U.S. Patent No. 5,399,346). Non-viral approaches may also be employed for the introduction of therapeutic DNA into diseased cells. For example, GPCR may be introduced into a cell by lipofection (Felgner et al., Proc. Natl. Acad. Sci.
15 USA 84:7413, 1987; Ono et al., Neurosci. Lett. 117:259, 1990; Brigham et al., Am. J. Med. Sci. 298:278, 1989; Staubinger et al., Meth. Enzymol. 101:512, 1983), asialorosanucoid-polylysine conjugation (Wu et al., J. Biol. Chem. 263:14621, 1988; Wu et al., J. Biol. Chem. 264:16985, 1989); or micro-injection under surgical conditions (Wolff et al., Science 247:1465, 1990).

20 Gene transfer can also be achieved using non-viral means requiring introduction of the nucleic acid *in vitro*. This method would, for example, include calcium phosphate, DEAE dextran, electroporation, and protoplast fusion. Liposomes may also be potentially beneficial for delivery of DNA into a cell.

Many methods for introducing vectors into cells or tissues are available and equally
25 suitable for use *in vivo*, *in vitro* and *ex vivo*. For *ex vivo* therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection and by liposome injections may be achieved using methods that are well known in the art. Transplantation of normal genes into the affected cells of a patient can also be useful therapy. In this procedure, a normal
30 gene encoding a GPCR polypeptide is transferred into a cultivatable cell type, either

exogenously or endogenously to the patient. These cells are then injected into the targeted tissue(s).

In the constructs described, GPCR cDNA expression can be directed from any suitable promoter (e.g., the human cytomegalovirus (CMV), simian virus 40 (SV40), or
5 metallothionein promoters), and regulated by any appropriate mammalian regulatory element. For example, if desired, enhancers known to preferentially direct gene expression in a particular cell may be used to direct GPCR expression. The enhancers used could include, without limitation, those that are characterized as tissue- or cell-specific in their expression. Alternatively, if a GPCR genomic clone is used as a therapeutic construct (for
10 example, following isolation by hybridization with the GPCR cDNA described above), regulation may be mediated by the cognate regulatory sequences or, if desired, by regulatory sequences derived from a heterologous source, including any of the promoters or regulatory elements described above.

Antisense or interfering RNA (RNAi) based strategies may be employed to explore
15 GPCR gene function and as a basis for therapeutic drug design. The principle is based on the hypothesis that sequence-specific suppression of gene expression can be achieved by intracellular hybridization between mRNA and a complementary antisense species. The formation of a hybrid RNA duplex may then interfere with the processing/transport/translation and/or stability of the target GPCR mRNA. Antisense and
20 interfering RNA strategies may use a variety of approaches including the use of antisense oligonucleotides and injection of antisense RNA. Phenotypic effects induced by antisense effects are based on changes in criteria such as protein levels, protein activity measurement, and target mRNA levels. Such technology is well known in the art, and sense or antisense oligomers, or larger fragments, can be designed from various locations along the coding or
25 control regions of sequences encoding a GPCR of the invention. In one example, the complementary oligonucleotide is designed from the most unique 5' sequence and used either to inhibit transcription by preventing promoter binding to the upstream nontranslated sequence or translation of a GPCR encoding transcript by preventing the ribosome from binding. Using an appropriate portion of the signal and 5' sequence, an effective antisense
30 oligonucleotide includes any 15-25 nucleotide spanning the region that translates into the

signal or 5' coding sequence of the polypeptide or 21-23 nucleotide spanning region for small interfering RNAs.

For example, gene therapy may also be accomplished by direct administration of antisense mRNA or small interfering RNAs to a cell that is expected to be involved in a
5 disease or disorder. The antisense mRNA may be produced and isolated by any standard technique, but it is most readily produced by *in vitro* transcription using an antisense cDNA under the control of a high efficiency promoter (e.g., the T7 promoter). Administration of antisense mRNA to cells can be carried out by any of the methods for direct nucleic acid administration described above.

10 Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Examples, which may be used, include engineered hammerhead motif ribozyme molecules that can specifically and efficiently catalyze endonucleolytic
15 cleavage of sequences encoding a GPCR of the invention.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites which include the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of, e.g., between 15 and 25 ribonucleotides corresponding to the region of the target gene
20 containing the cleavage site may be evaluated for secondary structural features that render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Other nucleic acid molecules that create triple helices within a gene have also been
25 demonstrated to block transcription.

Antisense molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by *in*
30 *vitro* and *in vivo* transcription of DNA sequences encoding a GPCR polypeptide of the

invention. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize antisense RNA constitutively or inducibly can be introduced into cell lines, cells, or tissues.

5 RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine,
10 queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine, which are not as easily recognized by endogenous endonucleases.

The GPCR sequences (Table 1) taught in the present invention facilitate the design of novel transcription factors for modulating GPCR expression in native cells and animals,
15 and cells transformed or transfected with GPCR polynucleotides. For example, the CYS2-HiS2 zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and are able to act as gene switches to modulate gene expression. Knowledge of the
20 particular GPCR target sequence of the present invention facilitates the engineering of zinc finger proteins specific for the target sequence using known methods such as a combination of structure-based modeling and screening of phage display libraries (Segal et al., Proc. Nat. Acad. Sci. USA 96:2758-2763 (1999); Liu et al., Proc. Nat. Acad. Sci. USA 94:5525-5530 (1997); Greisman et al., Science 275:657-661 (1997); Choo et al., J Mol Biol 273:525-
25 532 (1997)). Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence (Segal et al.). The artificial zinc finger repeats, designed based on GPCR sequences, are fused to activation or
30 repression domains to promote or suppress GPCR expression (Liu et al.). Alternatively, the

zinc finger domains can be fused to the TATA box-binding factor with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors (Kim et al, Proc. Nat. Acad. Sci. USA 94:3616-3620 (1997)). Such proteins and polynucleotides that encode them, have utility for modulating GPCR

5 expression in vivo in both native cells, animals and humans; and/or cells transfected with GPCR-encoding sequences. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences for use in therapeutics as alternatives to antisense or catalytic RNA methods

10 (McColl et al, Proc. Natl. Acad. Sci. USA 96:9521-9526 (1997); Wu et al, Proc. Natl. Acad. Sci. USA 92:344-348 (1995)). The present invention contemplates methods of designing such transcription factors based on the gene sequence of the invention, as well as customized zinc finger proteins, that are useful to modulate GPCR expression in cells (native or transformed) whose genetic complement includes these sequences.

15 An alternative strategy for inhibiting GPCR function using gene therapy involves intracellular expression of an anti-GPCR antibody or a portion of an anti-GPCR antibody. For example, the gene (or gene fragment) encoding a monoclonal antibody that specifically binds to a GPCR polypeptide and inhibits its biological activity may be placed under the transcriptional control of a cell type-specific gene regulatory sequence.

20

Sequences

Polynucleotide and polypeptide sequences for human and mouse GPCRs of the invention are listed in Table 35, submitted on compact disc. Putative transmembrane domains of the polypeptide sequences are underlined.

25

Other Embodiments

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety

as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth.

Other embodiments are within the claims.

5 What is claimed is:

Claims

1. A substantially pure polypeptide comprising a polypeptide sequence listed in Table 2.
2. A substantially pure polypeptide having at least 90% sequence identity to a polypeptide listed in Table 2.
3. The substantially pure polypeptide of claim 2, wherein said polypeptide has at least 95% identity to a polypeptide listed in Table 2.
4. The substantially pure polypeptide of claim 3, wherein said polypeptide has at least 97% identity to a polypeptide listed in Table 2.
5. The substantially pure polypeptide of claim 4, wherein said polypeptide has at least 98% identity to a polypeptide listed in Table 2.
6. The substantially pure polypeptide of claim 5, wherein said polypeptide has at least 99% identity to a polypeptide listed in Table 2.
7. A substantially pure polypeptide comprising a region having at least 90% sequence identity to a polypeptide listed in Table 2.
8. The substantially pure polypeptide of claim 7, wherein said region of said polypeptide has at least 95% identity to a polypeptide listed in Table 2.
9. The substantially pure polypeptide of claim 8, wherein said region of said polypeptide has at least 97% identity to a polypeptide listed in Table 2.
10. The substantially pure polypeptide of claim 9, wherein said region of said polypeptide has at least 98% identity to a polypeptide listed in Table 2.

11. The substantially pure polypeptide of claim 10, wherein said region of said polypeptide has at least 99% identity to a polypeptide listed in Table 2.
12. A substantially pure polypeptide, or fragment thereof, listed in Table 2.
13. A substantially pure polynucleotide encoding a polypeptide having a polypeptide sequence listed in Table 2.
14. A substantially pure polynucleotide encoding a polypeptide having at least 90% sequence identity to a polypeptide listed in Table 2.
15. The substantially pure polynucleotide of claim 14, wherein said polypeptide has at least 95% identity to a polypeptide listed in Table 2.
16. The substantially pure polynucleotide of claim 15, wherein said polypeptide has at least 97% identity to a polypeptide listed in Table 2.
17. The substantially pure polynucleotide of claim 16, wherein said polypeptide has at least 98% identity to a polypeptide listed in Table 2.
18. The substantially pure polynucleotide of claim 17, wherein said polypeptide has at least 99% identity to a polypeptide listed in Table 2.
19. A substantially pure polynucleotide encoding a polypeptide comprising a region having at least 90% sequence identity to a polypeptide listed in Table 2.
20. The substantially pure polynucleotide of claim 19, wherein said region of said polypeptide has at least 95% identity to a polypeptide listed in Table 2.
21. The substantially pure polynucleotide of claim 20, wherein said region of

said polypeptide has at least 97% identity to a polypeptide listed in Table 2.

22. The substantially pure polynucleotide of claim 21, wherein said region of said polypeptide has at least 98% identity to a polypeptide listed in Table 2.

23. The substantially pure polynucleotide of claim 22, wherein said region of said polypeptide has at least 99% identity to a polypeptide listed in Table 2.

24. A substantially pure polynucleotide encoding a polypeptide listed in Table 2.

25. A substantially pure polynucleotide listed in Table 2.

26. A substantially pure polynucleotide having at least 90% sequence identity to a polynucleotide listed in Table 2.

27. The substantially pure polynucleotide of claim 26, wherein said polynucleotide has at least 95% identity to a polynucleotide listed in Table 2.

28. The substantially pure polynucleotide of claim 27, wherein said polynucleotide has at least 97% identity to a polynucleotide listed in Table 2.

29. The substantially pure polynucleotide of claim 28, wherein said region of said polynucleotide has at least 98% identity to a polynucleotide listed in Table 2.

30. The substantially pure polynucleotide of claim 29, wherein said region of said polynucleotide has at least 99% identity to a polynucleotide listed in Table 2.

31. A substantially pure polynucleotide being the reverse complement of the polynucleotide listed in Table 2.

32. A substantially pure polynucleotide having at least 90% sequence identity to the reverse complement of polynucleotide listed in Table 2.

33. The substantially pure polynucleotide of claim 32, wherein said polynucleotide has at least 95% identity to the reverse complement of polynucleotide listed in Table 2.

34. The substantially pure polynucleotide of claim 33, wherein said polynucleotide has at least 97% identity to the reverse complement of polynucleotide listed in Table 2.

35. The substantially pure polynucleotide of claim 34, wherein said region of said polynucleotide has at least 98% identity to the reverse complement of polynucleotide listed in Table 2.

36. The substantially pure polynucleotide of claim 35, wherein said region of said polynucleotide has at least 99% identity to the reverse complement of polynucleotide listed in Table 2.

37. A method for determining whether a patient has an increased risk for developing a neurological disease or disorder, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a neurological disease or disorder.

38. A method for determining whether a patient has an increased risk for developing a neurological disease or disorder, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a neurological disease or disorder.

39. A method for determining whether a patient has an increased risk for developing a neurological disease or disorder, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a neurological disease or disorder.

40. The method of claim 39, wherein said expression is determined by measuring levels of said GPCR polypeptide.

41. The method of claim 39, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

42. A method for determining whether a patient has an increased risk for developing a neurological disease or disorder, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, wherein the presence of said polymorphism associated with a neurological disease or disorder indicates the person has an altered risk for developing a neurological disease or disorder.

43. A method for determining whether a patient has an increased risk for developing a disease or disorder of the adrenal gland, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the adrenal gland.

44. A method for determining whether a patient has an increased risk for developing a disease or disorder of the adrenal gland, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, wherein

an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the adrenal gland.

45. A method for determining whether a patient has an increased risk for developing a disease or disorder of the adrenal gland, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the adrenal gland.

46. The method of claim 45, wherein said expression is determined by measuring levels of said GPCR polypeptide.

47. The method of claim 45, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

48. A method for determining whether a patient has an increased risk for developing a disease or disorder of the adrenal gland, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the adrenal gland indicates the person has an altered risk for developing a disease or disorder of the adrenal gland.

49. A method for determining whether a patient has an increased risk for developing a disease or disorder of the colon, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the colon.

50. A method for determining whether a patient has an increased risk for

developing a disease or disorder of the colon, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the colon.

51. A method for determining whether a patient has an increased risk for developing a disease or disorder of the colon, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the colon.

52. The method of claim 51, wherein said expression is determined by measuring levels of said GPCR polypeptide.

53. The method of claim 51, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

54. A method for determining whether a patient has an increased risk for developing a disease or disorder of the colon, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the colon indicates the person has an altered risk for developing a disease or disorder of the colon.

55. A method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a cardiovascular

disease or disorder.

56. A method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a cardiovascular disease or disorder.

57. A method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a cardiovascular disease or disorder.

58. The method of claim 57, wherein said expression is determined by measuring levels of said GPCR polypeptide.

59. The method of claim 57, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

60. A method for determining whether a patient has an increased risk for developing a cardiovascular disease or disorder, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, wherein the presence of said polymorphism associated with a cardiovascular disease or disorder indicates the person has an altered risk for developing a cardiovascular disease or disorder.

61. A method for determining whether a patient has an increased risk for developing a disease or disorder of the intestine, said method comprising determining

the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the intestine.

62. A method for determining whether a patient has an increased risk for developing a disease or disorder of the intestine, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the intestine.

63. A method for determining whether a patient has an increased risk for developing a disease or disorder of the intestine, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the intestine.

64. The method of claim 63, wherein said expression is determined by measuring levels of said GPCR polypeptide.

65. The method of claim 63, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

66. A method for determining whether a patient has an increased risk for developing a disease or disorder of the intestine, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the intestine indicates the person has an altered risk for developing a disease or disorder of the intestine.

67. A method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the kidney.

68. A method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the kidney.

69. A method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the kidney.

70. The method of claim 69, wherein said expression is determined by measuring levels of said GPCR polypeptide.

71. The method of claim 69, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

72. A method for determining whether a patient has an increased risk for developing a disease or disorder of the kidney, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical

to a polypeptide listed in Tables 19 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the kidney indicates the person has an altered risk for developing a disease or disorder of the kidney.

73. A method for determining whether a patient has an increased risk for developing a disease or disorder of the liver, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the liver.

74. A method for determining whether a patient has an increased risk for developing a disease or disorder of the liver, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the liver.

75. A method for determining whether a patient has an increased risk for developing a disease or disorder of the liver, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the liver.

76. The method of claim 75, wherein said expression is determined by measuring levels of said GPCR polypeptide.

77. The method of claim 75, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

78. A method for determining whether a patient has an increased risk for developing a disease or disorder of the liver, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the liver indicates the person has an altered risk for developing a disease or disorder of the liver.

79. A method for determining whether a patient has an increased risk for developing a lung disease or disorder, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a lung disease or disorder.

80. A method for determining whether a patient has an increased risk for developing a lung disease or disorder, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a lung disease or disorder.

81. A method for determining whether a patient has an increased risk for developing a lung disease or disorder, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a lung disease or disorder.

82. The method of claim 81, wherein said expression is determined by measuring levels of said GPCR polypeptide.

83. The method of claim 81, wherein said expression is determined by

measuring levels of RNA encoding said GPCR polypeptide.

84. A method for determining whether a patient has an increased risk for developing a lung disease or disorder, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, wherein the presence of said polymorphism associated with a lung disease or disorder indicates the person has an altered risk for developing a lung disease or disorder.

85. A method for determining whether a patient has an increased risk for developing a muscular disease or disorder, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a muscular disease or disorder.

86. A method for determining whether a patient has an increased risk for developing a muscular disease or disorder, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a muscular disease or disorder.

87. A method for determining whether a patient has an increased risk for developing a muscular disease or disorder, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a muscular disease or disorder.

88. The method of claim 87, wherein said expression is determined by

measuring levels of said GPCR polypeptide.

89. The method of claim 87, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

90. A method for determining whether a patient has an increased risk for developing a muscular disease or disorder, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, wherein the presence of said polymorphism associated with a muscular disease or disorder indicates the person has an altered risk for developing a muscular disease or disorder.

91. A method for determining whether a patient has an increased risk for developing a disease or disorder of the ovary, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the ovary.

92. A method for determining whether a patient has an increased risk for developing a disease or disorder of the ovary, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the ovary.

93. A method for determining whether a patient has an increased risk for developing a disease or disorder of the ovary, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for

developing a disease or disorder of the ovary.

94. The method of claim 93, wherein said expression is determined by measuring levels of said GPCR polypeptide.

95. The method of claim 93, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

96. A method for determining whether a patient has an increased risk for developing a disease or disorder of the ovary, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the ovary indicates the person has an altered risk for developing a disease or disorder of the ovary.

97. A method for determining whether a patient has an increased risk for developing a blood disease or disorder, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a blood disease or disorder.

98. A method for determining whether a patient has an increased risk for developing a blood disease or disorder, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a blood disease or disorder.

99. A method for determining whether a patient has an increased risk for developing a blood disease or disorder, said method comprising measuring in said

patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a blood disease or disorder.

100. The method of claim 99, wherein said expression is determined by measuring levels of said GPCR polypeptide.

101. The method of claim 99, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

102. A method for determining whether a patient has an increased risk for developing a blood disease or disorder, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, wherein the presence of said polymorphism associated with a blood disease or disorder indicates the person has an altered risk for developing a blood disease or disorder.

103. A method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the prostate.

104. A method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the prostate.

105. A method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the prostate.

106. The method of claim 105, wherein said expression is determined by measuring levels of said GPCR polypeptide.

107. The method of claim 105, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

108. A method for determining whether a patient has an increased risk for developing a disease or disorder of the prostate, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the prostate indicates the person has an altered risk for developing a disease or disorder of the prostate.

109. A method for determining whether a patient has an increased risk for developing a disease or disorder of the skin, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the skin.

110. A method for determining whether a patient has an increased risk for developing a disease or disorder of the skin, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR

polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the skin.

111. A method for determining whether a patient has an increased risk for developing a disease or disorder of the skin, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the skin.

112. The method of claim 111, wherein said expression is determined by measuring levels of said GPCR polypeptide.

113. The method of claim 111, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

114. A method for determining whether a patient has an increased risk for developing a disease or disorder of the skin, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the skin indicates the person has an altered risk for developing a disease or disorder of the skin.

115. A method for determining whether a patient has an increased risk for developing a disease or disorder of the spleen, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the spleen.

116. A method for determining whether a patient has an increased risk for developing a disease or disorder of the spleen, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the spleen.

117. A method for determining whether a patient has an increased risk for developing a disease or disorder of the spleen, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the spleen.

118. The method of claim 117, wherein said expression is determined by measuring levels of said GPCR polypeptide.

119. The method of claim 117, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

120. A method for determining whether a patient has an increased risk for developing a disease or disorder of the spleen, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the spleen indicates the person has an altered risk for developing a disease or disorder of the spleen.

121. A method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, wherein the presence

of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the stomach.

122. A method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the stomach.

123. A method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the stomach.

124. The method of claim 123, wherein said expression is determined by measuring levels of said GPCR polypeptide.

125. The method of claim 123, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

126. A method for determining whether a patient has an increased risk for developing a disease or disorder of the stomach, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the stomach indicates the person has an altered risk for developing a disease or disorder of the stomach.

127. A method for determining whether a patient has an increased risk for

developing a disease or disorder of the testes, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the testes.

128. A method for determining whether a patient has an increased risk for developing a disease or disorder of the testes, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the testes.

129. A method for determining whether a patient has an increased risk for developing a disease or disorder of the testes, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the testes.

130. The method of claim 129, wherein said expression is determined by measuring levels of said GPCR polypeptide.

131. The method of claim 129, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

132. A method for determining whether a patient has an increased risk for developing a disease or disorder of the testes, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the testes indicates the person has an altered risk

for developing a disease or disorder of the testes.

133. A method for determining whether a patient has an increased risk for developing a disease or disorder of the thymus, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the thymus.

134. A method for determining whether a patient has an increased risk for developing a disease or disorder of the thymus, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the thymus.

135. A method for determining whether a patient has an increased risk for developing a disease or disorder of the thymus, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the thymus.

136. The method of claim 135, wherein said expression is determined by measuring levels of said GPCR polypeptide.

137. The method of claim 135, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

138. A method for determining whether a patient has an increased risk for

developing a disease or disorder of the thymus, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the thymus indicates the person has an altered risk for developing a disease or disorder of the thymus.

139. A method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the thyroid.

140. A method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the thyroid.

141. A method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the thyroid.

142. The method of claim 141, wherein said expression is determined by measuring levels of said GPCR polypeptide.

143. The method of claim 141, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

144. A method for determining whether a patient has an increased risk for developing a disease or disorder of the thyroid, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the thyroid indicates the person has an altered risk for developing a disease or disorder of the thyroid.

145. A method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the uterus.

146. A method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the uterus.

147. A method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the uterus.

148. The method of claim 147, wherein said expression is determined by measuring levels of said GPCR polypeptide.

149. The method of claim 147, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

150. A method for determining whether a patient has an increased risk for developing a disease or disorder of the uterus, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, wherein the presence of said polymorphism associated with a disease or disorder of the uterus indicates the person has an altered risk for developing a disease or disorder of the uterus.

151. A method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the pancreas.

152. A method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the pancreas.

153. A method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein altered levels in said

expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the pancreas.

154. The method of claim 153, wherein said expression is determined by measuring levels of said GPCR polypeptide.

155. The method of claim 153, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

156. A method for determining whether a patient has an increased risk for developing a disease or disorder of the pancreas, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said polymorphism associated with a disease or disorder of the pancreas indicates the person has an altered risk for developing a disease or disorder of the pancreas.

157. A method for determining whether a patient has an increased risk for developing a disease or disorder of the bone and joints, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the bone and joints.

158. A method for determining whether a patient has an increased risk for developing a disease or disorder of the bone and joints, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the bone and joints.

159. A method for determining whether a patient has an increased risk for

developing a disease or disorder of the bone and joints, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the bone and joints.

160. The method of claim 159, wherein said expression is determined by measuring levels of said GPCR polypeptide.

161. The method of claim 159, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

162. A method for determining whether a patient has an increased risk for developing a disease or disorder of the bone and joints, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said polymorphism associated with a disease or disorder of the bone and joints indicates the person has an altered risk for developing a disease or disorder of the bone and joints.

163. A method for determining whether a patient has an increased risk for developing a disease or disorder of the breast, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the breast.

164. A method for determining whether a patient has an increased risk for developing a disease or disorder of the breast, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an

increased risk for developing a disease or disorder of the breast.

165. A method for determining whether a patient has an increased risk for developing a disease or disorder of the breast, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the breast.

166. The method of claim 165, wherein said expression is determined by measuring levels of said GPCR polypeptide.

167. The method of claim 165, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

168. A method for determining whether a patient has an increased risk for developing a disease or disorder of the breast, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said polymorphism associated with a disease or disorder of the breast indicates the person has an altered risk for developing a disease or disorder of the breast.

169. A method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said mutation indicates that said patient has an increased risk for developing a disease or disorder of the immune system.

170. A method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system, said method comprising

measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a disease or disorder of the immune system.

171. A method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a disease or disorder of the immune system.

172. The method of claim 171, wherein said expression is determined by measuring levels of said GPCR polypeptide.

173. The method of claim 171, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

174. A method for determining whether a patient has an increased risk for developing a disease or disorder of the immune system, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said polymorphism associated with a disease or disorder of the immune system indicates the person has an altered risk for developing a disease or disorder of the immune system.

175. A method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder, said method comprising determining the presence of a mutation in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said mutation indicates that said patient has an increased risk for developing a metabolic or nutritive disease or disorder.

176. A method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder, said method comprising measuring in said patient or in a cell from said patient the level of biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein an altered level in said biological activity, relative to normal, indicates that said patient has an increased risk for developing a metabolic or nutritive disease or disorder.

177. A method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder, said method comprising measuring in said patient or in a cell from said patient the expression of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein altered levels in said expression, relative to normal levels, indicates that said patient has an increased risk for developing a metabolic or nutritive disease or disorder.

178. The method of claim 177, wherein said expression is determined by measuring levels of said GPCR polypeptide.

179. The method of claim 177, wherein said expression is determined by measuring levels of RNA encoding said GPCR polypeptide.

180. A method for determining whether a patient has an increased risk for developing a metabolic or nutritive disease or disorder, comprising determining the presence of a polymorphism in the patient's gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, wherein the presence of said polymorphism associated with a metabolic or nutritive disease or disorder indicates the person has an altered risk for developing a metabolic or nutritive disease or disorder.

181. A method of treating or preventing a neurological disease or disorder in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one

of Tables 3-14 and 33.

182. A method of treating or preventing a neurological disease or disorder in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33.

183. A method of treating or preventing a neurological disease or disorder in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33.

184. A method of treating or preventing a disease or disorder of the adrenal gland in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33.

185. A method of treating or preventing a disease or disorder of the adrenal gland in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33.

186. A method of treating or preventing a disease or disorder of the adrenal gland in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33.

187. A method of treating or preventing a disease or disorder of the colon in a patient, said method comprising administering to said patient a nucleic acid molecule

encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33.

188. A method of treating or preventing a disease or disorder of the colon in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33.

189. A method of treating or preventing a disease or disorder of the colon in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33.

190. A method of treating or preventing a cardiovascular disease or disorder in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33.

191. A method of treating or preventing a cardiovascular disease or disorder in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33.

192. A method of treating or preventing a cardiovascular disease or disorder in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33.

193. A method of treating or preventing a disease or disorder of the intestine in a

patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33.

194. A method of treating or preventing a disease or disorder of the intestine in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33.

195. A method of treating or preventing a disease or disorder of the intestine in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33.

196. A method of treating or preventing a disease or disorder of the kidney in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33.

197. A method of treating or preventing a disease or disorder of the kidney in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33.

198. A method of treating or preventing a disease or disorder of the kidney in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33.

199. A method of treating or preventing a disease or disorder of the liver in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33.

200. A method of treating or preventing a disease or disorder of the liver in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33.

201. A method of treating or preventing a disease or disorder of the liver in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33.

202. A method of treating or preventing a lung disease or disorder in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33.

203. A method of treating or preventing a lung disease or disorder in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33.

204. A method of treating or preventing a lung disease or disorder in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33.

205. A method of treating or preventing a muscular disease or disorder in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33.

206. A method of treating or preventing a muscular disease or disorder in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33.

207. A method of treating or preventing a muscular disease or disorder in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33.

208. A method of treating or preventing a disease or disorder of the ovary in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33.

209. A method of treating or preventing a disease or disorder of the ovary in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33.

210. A method of treating or preventing a disease or disorder of the ovary in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33.

211. A method of treating or preventing a blood disease or disorder in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33.

212. A method of treating or preventing a blood disease or disorder in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33.

213. A method of treating or preventing a blood disease or disorder in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33.

214. A method of treating or preventing a disease or disorder of the prostate in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33.

215. A method of treating or preventing a disease or disorder of the prostate in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33.

216. A method of treating or preventing a disease or disorder of the prostate in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33.

217. A method of treating or preventing a disease or disorder of the skin in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33.

218. A method of treating or preventing a disease or disorder of the skin in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33.

219. A method of treating or preventing a disease or disorder of the skin in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33.

220. A method of treating or preventing a disease or disorder of the spleen in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33.

221. A method of treating or preventing a disease or disorder of the spleen in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33.

222. A method of treating or preventing a disease or disorder of the spleen in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a

polypeptide listed in Tables 27 and 33.

223. A method of treating or preventing a disease or disorder of the stomach in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33.

224. A method of treating or preventing a disease or disorder of the stomach in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33.

225. A method of treating or preventing a disease or disorder of the stomach in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33.

226. A method of treating or preventing a disease or disorder of the testes in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33.

227. A method of treating or preventing a disease or disorder of the testes in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33.

228. A method of treating or preventing a disease or disorder of the testes in a patient, said method comprising administering to said patient a compound that

modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33.

229. A method of treating or preventing a disease or disorder of the thymus in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33.

230. A method of treating or preventing a disease or disorder of the thymus in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33.

231. A method of treating or preventing a disease or disorder of the thymus in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33.

232. A method of treating or preventing a disease or disorder of the thyroid in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33.

233. A method of treating or preventing a disease or disorder of the thyroid in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33.

234. A method of treating or preventing a disease or disorder of the thyroid in a

patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33.

235. A method of treating or preventing a disease or disorder of the uterus in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33.

236. A method of treating or preventing a disease or disorder of the uterus in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33.

237. A method of treating or preventing a disease or disorder of the uterus in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33.

238. A method of treating or preventing a disease or disorder of the pancreas in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

239. A method of treating or preventing a disease or disorder of the pancreas in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

240. A method of treating or preventing a disease or disorder of the pancreas in

a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

241. A method of treating or preventing a disease or disorder of the bone and joint in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

242. A method of treating or preventing a disease or disorder of the bone and joint in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

243. A method of treating or preventing a disease or disorder of the bone and joint in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

244. A method of treating or preventing a disease or disorder of the breast in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

245. A method of treating or preventing a disease or disorder of the breast in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

246. A method of treating or preventing a disease or disorder of the breast in a

patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

247. A method of treating or preventing a disease or disorder of the immune system in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

248. A method of treating or preventing a disease or disorder of the immune system in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

249. A method of treating or preventing a disease or disorder of the immune system in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

250. A method of treating or preventing a metabolic or nutritive disease or disorder in a patient, said method comprising administering to said patient a nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

251. A method of treating or preventing a metabolic or nutritive disease or disorder in a patient, said method comprising administering to said patient an expression vector comprising a nucleic acid molecule operably linked to a promoter, said nucleic acid molecule encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

252. A method of treating or preventing a metabolic or nutritive disease or disorder in a patient, said method comprising administering to said patient a compound that modulates the biological activity of a GPCR polypeptide substantially identical to a polypeptide listed in Table 1.

253. A method for identifying a compound that may be useful for the treatment or prevention of a neurological disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a neurological disease or disorder.

254. A method for identifying a compound that may be useful for the treatment or prevention of a neurological disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33 with a candidate compound; and
- (b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a neurological disease or disorder.

255. A method for identifying a compound that may be useful for the treatment or prevention of a neurological disease or disorder, said method comprising the steps of:

- (a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, operably linked to a reporter gene;

- (b) contacting said nucleic acid molecule with a candidate compound; and
- (c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a neurological disease or disorder.

256. A method for identifying a compound that may be useful for the treatment or prevention of a neurological disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a neurological disease or disorder.

257. A method for identifying a compound that may be useful for the treatment or prevention of a neurological disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a neurological disease or disorder.

258. A method for identifying a compound that may be useful for the treatment or prevention of a neurological disease or disorder, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in any one of Tables 3-14 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;

(b) contacting said polypeptides with a candidate compound; and
(c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a neurological disease or disorder.

259. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland, said method comprising the steps of:

(a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33 with a candidate compound; and
(b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the adrenal gland.

260. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland, said method comprising the steps of:

(a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell, wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland.

261. A method for identifying a compound that may be useful for the treatment

or prevention of a disease or disorder of the adrenal gland, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland.

262. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland.

263. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland.

264. A method for identifying a compound that may be useful for the treatment

or prevention of a disease or disorder of the adrenal gland, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 15 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the adrenal gland.

265. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the colon, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the colon.

266. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the colon, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33 with a candidate compound; and

- (b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the colon.

267. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the colon, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the colon.

268. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the colon, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the colon.

269. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the colon, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the colon.

270. A method for identifying a compound that may be useful for the treatment

or prevention of a disease or disorder of the colon, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 16 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the colon.

271. A method for identifying a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a cardiovascular disease or disorder.

272. A method for identifying a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33 with a candidate compound; and

- (b) measuring expression of said GPCR polypeptide in said cell, wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a cardiovascular disease or

disorder.

273. A method for identifying a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder.

274. A method for identifying a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder.

275. A method for identifying a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment

or prevention of a cardiovascular disease or disorder.

276. A method for identifying a compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 17 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a cardiovascular disease or disorder.

277. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33 with a candidate compound; and
 - (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,
- wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the intestine.

278. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell, wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine.

279. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine.

280. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine.

281. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in

Tables 18 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine.

282. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the intestine, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 18 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the intestine.

283. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the kidney.

284. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide

substantially identical to a polypeptide listed in Tables 19 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney.

285. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney.

286. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney.

287. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables

19 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney.

288. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the kidney, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 19 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the kidney.

289. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the liver, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the liver.

290. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the liver, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33 with a candidate

compound; and

(b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the liver.

291. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the liver, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the liver.

292. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the liver, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the liver.

293. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the liver, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, and disposed in a lipid membrane with a candidate compound; and

determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the liver.

294. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the liver, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 20 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the liver.

295. A method for identifying a compound that may be useful for the treatment or prevention of a lung disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a lung disease or disorder.

296. A method for identifying a compound that may be useful for the treatment or prevention of a lung disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,
wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a lung disease or disorder.

297. A method for identifying a compound that may be useful for the treatment or prevention of a lung disease or disorder, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a lung disease or disorder.

298. A method for identifying a compound that may be useful for the treatment or prevention of a lung disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a lung disease or disorder.

299. A method for identifying a compound that may be useful for the treatment or prevention of a lung disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide

wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a lung disease or disorder.

300. A method for identifying a compound that may be useful for the treatment or prevention of a lung disease or disorder, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 21 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a lung disease or disorder.

301. A method for identifying a compound that may be useful for the treatment or prevention of a muscular disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a muscular disease or disorder.

302. A method for identifying a compound that may be useful for the treatment or prevention of a muscular disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33 with a candidate compound; and
- (b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a muscular disease or disorder.

303. A method for identifying a compound that may be useful for the treatment or prevention of a muscular disease or disorder, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a muscular disease or disorder.

304. A method for identifying a compound that may be useful for the treatment or prevention of a muscular disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a muscular disease or disorder.

305. A method for identifying a compound that may be useful for the treatment or prevention of a muscular disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide

identifies said candidate compound as a compound that may be useful for the treatment or prevention of a muscular disease or disorder.

306. A method for identifying a compound that may be useful for the treatment or prevention of a muscular disease or disorder, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 22 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a muscular disease or disorder.

307. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell, wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the ovary.

308. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33 with a candidate compound; and
- (b) measuring expression of said GPCR polypeptide in said cell, wherein altered expression of said GPCR polypeptide, relative to a cell not

contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary.

309. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary.

310. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary.

311. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment

or prevention of a disease or disorder of the ovary.

312. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the ovary, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 23 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the ovary.

313. A method for identifying a compound that may be useful for the treatment or prevention of a blood disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33 with a candidate compound; and
 - (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,
- wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a blood disease or disorder.

314. A method for identifying a compound that may be useful for the treatment or prevention of a blood disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33 with a candidate compound; and
 - (b) measuring expression of said GPCR polypeptide in said cell,
- wherein altered expression of said GPCR polypeptide, relative to a cell not

contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a blood disease or disorder.

315. A method for identifying a compound that may be useful for the treatment or prevention of a blood disease or disorder, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a blood disease or disorder.

316. A method for identifying a compound that may be useful for the treatment or prevention of a blood disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a blood disease or disorder.

317. A method for identifying a compound that may be useful for the treatment or prevention of a blood disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment

or prevention of a blood disease or disorder.

318: A method for identifying a compound that may be useful for the treatment or prevention of a blood disease or disorder, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 24 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a blood disease or disorder.

319. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the prostate.

320. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33 with a candidate compound; and
- (b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate.

321. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate.

322. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate.

323. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide

wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate.

324. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the prostate, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 25 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the prostate.

325. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the skin, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the skin.

326. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the skin, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,
wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the skin.

327. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the skin, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the skin.

328. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the skin, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the skin.

329. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the skin, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide

wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the skin.

330. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the skin, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 26 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the skin.

331. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the spleen.

332. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33 with a candidate compound; and
- (b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen.

333. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen.

334. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen.

335. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide

identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen.

336. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the spleen, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 27 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the spleen.

337. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the stomach.

338. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,
wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach.

339. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach.

340. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach.

341. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in

Tables 28 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach.

342. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the stomach, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 28 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the stomach.

343. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the testes, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33 with a candidate compound; and
 - (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,
- wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the testes.

344. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the testes, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide

substantially identical to a polypeptide listed in Tables 29 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the testes.

345. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the testes, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the testes.

346. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the testes, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the testes.

347. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the testes, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables

29 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the testes.

348. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the testes, said method comprising the steps of:

(a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 29 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;

(b) contacting said polypeptides with a candidate compound; and

(c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the testes.

349. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus, said method comprising the steps of:

(a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33 with a candidate compound; and

(b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the thymus.

350. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus, said method comprising the steps of:

(a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus.

351. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus.

352. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus.

353. A method for identifying a compound that may be useful for the treatment

or prevention of a disease or disorder of the thymus, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus.

354. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thymus, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 30 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the thymus.

355. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the thyroid.

356. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33 with a candidate compound; and
- (b) measuring expression of said GPCR polypeptide in said cell, wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid.

357. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid, said method comprising the steps of:

- (a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, operably linked to a reporter gene;
- (b) contacting said nucleic acid molecule with a candidate compound; and
- (c) measuring expression of said reporter gene, wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid.

358. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder

of the thyroid.

359. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid.

360. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 31 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the thyroid.

361. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell, wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a

compound that may be useful for the treatment of a disease or disorder of the uterus.

362. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus, said method comprising the steps of:

(a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus.

363. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus.

364. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder

of the uterus.

365. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus.

366. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the uterus, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Tables 32 and 33, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the uterus.

367. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a

compound that may be useful for the treatment of a disease or disorder of the pancreas.

368. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas, said method comprising the steps of:

(a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell, wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas.

369. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas.

370. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate

compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas.

371. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas.

372. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the pancreas.

373. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said

cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the bone and joints.

374. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints, said method comprising the steps of:

(a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,
wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints.

375. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints.

376. A method for identifying a compound that may be useful for the treatment

or prevention of a disease or disorder of the bone and joints, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints.

377. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints.

378. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints, said method comprising the steps of:

(a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, and (ii) a second polypeptide that interacts with said GPCR polypeptide;

(b) contacting said polypeptides with a candidate compound; and

(c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the bone and joints.

379. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the breast, said method comprising the steps of:

(a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and

(b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the breast.

380. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the breast, said method comprising the steps of:

(a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the breast.

381. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the breast, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the breast.

382. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the breast, said method comprising the steps of

contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the breast.

383. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the breast, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the breast.

384. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the breast, said method comprising the steps of:

- (a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, and (ii) a second polypeptide that interacts with said GPCR polypeptide;
- (b) contacting said polypeptides with a candidate compound; and
- (c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the breast.

385. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and

(b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a disease or disorder of the immune system.

386. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system, said method comprising the steps of:

(a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and

(b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system.

387. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system, said method comprising the steps of:

(a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a reporter gene;

(b) contacting said nucleic acid molecule with a candidate compound; and

(c) measuring expression of said reporter gene,

wherein altered reporter gene expression, relative to a control not contacted with said candidate compound, indicates that said candidate compound is a compound that a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system.

388. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system.

389. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system.

390. A method for identifying a compound that may be useful for the treatment or prevention of a disease or disorder of the immune system, said method comprising the steps of:

(a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, and (ii) a second polypeptide that interacts with said GPCR polypeptide;

(b) contacting said polypeptides with a candidate compound; and

(c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second polypeptide identifies said candidate compound that may be useful for the treatment or prevention of a disease or disorder of the immune system.

391. A method for identifying a compound that may be useful for the treatment

or prevention of metabolic or nutritive disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and
- (b) measuring the biological activity of said GPCR polypeptide expressed in said cell,

wherein altered biological activity of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder.

392. A method for identifying a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder, said method comprising the steps of:

- (a) contacting a cell expressing a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 with a candidate compound; and
- (b) measuring expression of said GPCR polypeptide in said cell,

wherein altered expression of said GPCR polypeptide, relative to a cell not contacted with said compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder.

393. A method for identifying a compound that may be useful for the treatment or prevention of metabolic or nutritive disease or disorder, said method comprising the steps of:

- (a) providing a nucleic acid molecule comprising a promoter for a gene encoding a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 operably linked to a reporter gene;
 - (b) contacting said nucleic acid molecule with a candidate compound; and
 - (c) measuring expression of said reporter gene,
- wherein altered reporter gene expression, relative to a control not contacted with

said candidate compound, indicates that said candidate compound is a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder.

394. A method for identifying a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide, wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder.

395. A method for identifying a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder, said method comprising the steps of contacting a GPCR polypeptide substantially identical to a polypeptide listed in Table 1 and disposed in a lipid membrane with a candidate compound; and determining whether said candidate compound interacts with said GPCR polypeptide wherein interaction between said candidate compound and said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder.

396. A method for identifying a compound that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder, said method comprising the steps of:

(a) providing (i) a GPCR polypeptide substantially identical to a polypeptide listed in Table 1, and (ii) a second polypeptide that interacts with said GPCR polypeptide;

(b) contacting said polypeptides with a candidate compound; and

(c) measuring interaction of said GPCR polypeptide and said second polypeptide, wherein an alteration in interaction of said GPCR polypeptide and said second

polypeptide identifies said candidate compound as one that may be useful for the treatment or prevention of a metabolic or nutritive disease or disorder.

397. The method of any of claims 37-42, 181-183, and 253-258, wherein said neurological disease or disorder is selected from the group consisting of abetalipoproteinemia, abnormal social behaviors, absence (petit mal) epilepsy, absence seizures, abulia, acalculia, acidophilic adenoma, acoustic neuroma, acquired aphasia, acquired aphasia with epilepsy (Landau-Kleffner syndrome) specific reading disorder, acquired epileptic aphasia, acromegalic neuropathy, acromegaly, action myoclonus-renal insufficiency syndrome, acute autonomic neuropathy, acute cerebellar ataxia in children, acute depression, acute disseminated encephalomyelitis, acute idiopathic sensory neuronopathy, acute intermittent porphyria, acute mania, acute mixed episode, acute pandysautonomia, acute polymorphic disorder with symptoms of schizophrenia, acute polymorphic psychotic disorder without symptoms of schizophrenia, acute purulent meningitis, addiction, Addison syndrome, adenovirus serotypes, adjustment disorders, adrenal hyperfunction, adrenal hypofunction, adrenoleukodystrophy, adrenomyeloneuropathy, advanced sleep-phase syndrome, affective disorder syndromes, agenesis of the corpus callosum, agnosia, agoraphobia, agraphia, agyria, agyria-pachygyria, ahylognosia, Aicardi syndrome, AIDS, akathisia, akinesia, akinetic mutism, akinetopsia, alcohol abuse, alcohol dependence syndrome, alcohol neuropathy, alcohol related disorders, alcoholic amblyopia, alcoholic blacknocks, alcoholic cerebellar degeneration, alcoholic dementia, alcoholic hallucinosis, alcoholic polyneuropathy, alcohol-induced anxiety disorders, alcohol-induced dementia, alcohol-induced mood disorders, alcohol-induced psychosis, alcoholism, Alexander's syndrome, alexia, alexia with agraphia, alexia without agraphia, alien hand syndrome, Alper's disease, altered sexuality syndromes, alternating hemiplegia, Alzheimer's disease, Alzheimer-like senile dementia, Alzheimer-like juvenile dementia, amenorrhea, aminoacidurias, amnesia, amnesia for offences, amok-type reactions, amorphognosia, amphetamine addiction, amphetamine or amphetamine-like related disorders, amphetamine withdrawal, amyloid neuropathy, amyotrophic lateral sclerosis, anencephaly, aneurysms, angioblastic meningiomas, Angelman's syndrome, anhidrosis, anisocoria, anomia, anomic aphasia,

anorexia nervosa, anosmia, anosognosia, anterior cingulate syndrome, anterograde amnesia, antibiotic-induced neuromuscular blockade, antisocial personality disorder, Anton's syndrome, anxiety and obsessive-compulsive disorder syndromes, anxiety disorders, apathy syndromes, aphasia, aphemia, aplasia, apnea, apraxia, arachnoid cyst, archicerebellar syndrome, Arnold-Chiari malformation, arousal disorders, arrhinencephaly, arsenic poisoning, arteriosclerotic Parkinsonism, arteriovenous aneurysm, arteriovenous malformations, aseptic meningeal reaction, Asperger's syndrome, astereognosis, asthenia, astrocytomas, asymbolia, asynergia, ataque de nervios, ataxia, ataxia telangiectasia, ataxic cerebral palsy, ataxic dysarthria, athetosis, atonia, atonic seizures, attention deficit disorder, attention-deficit and disruptive behavior disorders, attention-deficit hyperkinetic disorders, atypical Alzheimer's disease, atypical autism, autism, autism spectrum disorder, avoidant personality disorder, axial dementias, bacterial endocarditis, bacterial infections, Balint's syndrome, ballism, balo disease, basophilic adenoma, Bassen-Knock outnznweig syndrome, Batten disease, battered woman syndrome, Behçet syndrome, Bell' palsy, benign essential tremor, benign focal epilepsies of childhood, benign intracranial hypertension, benxodiazepine dependence, bilateral cortical dysfunction, Binswanger's disease, bipolar disorder, bipolar type 1 disorder, bipolar type 2 disorder, blepharospasm, body dysmorphic disorder, Bogaert-Bertrand disease, Bogarad syndrome, borderline personality disorder, botulism, Bouffée Délirante-type reactions, brachial neuropathy, bradycardia, bradykinesia, brain abscess, brain edema, brain fog, brain stem glioma, brainstem encephalitis, brief psychotic disorder, broca's aphasia, brucellosis, bulimia, bulimia nervosa, butterfly glioma, cachexia, caffeine related disorders, califormia encephalitis, callosal agenesis, Canavan's syndrome, cancer pain, cannabis dependence, cannabis flashbacks, cannabis psychosis, cannabis related disorders, carcinoma-associated retinopathy, cardiac arrest, cavernous malformations, cellular (cytotoxic) edema, central facial paresis, central herniation syndrome, central neurogenic hyperventilation, central pontine myelinolysis, central post-stroke syndrome (thalamic pain syndrome), cerebellar hemorrhage, cerebellar tonsillar herniation syndrome, cerebral amyloid (congophilic) angiopathy, cerebral hemorrhage, cerebral malaria, cerebral palsy, cerebral subdural empyema, cerebrotendinous xanthomatosis,

cerebrovascular disorders, cervical tumors, cestodes, Charcot-Carrie-tooth disease, Chediak-Cigashi disease, Cheiro-oral syndrome, chiari malformation with hydrocephalus, childhood disintegrative disorder, childhood feeding problems, childhood sleep problems, cholesteatomas, chordomas, chorea, chorea gravidarum, choreoathetosis, chromophobe adenoma, chromosomal disorders, chronic biplar major depression, chronic bipolar disorder, chronic demyelinating polyneuritis, chronic depression, chronic fatigue syndrome, chronic gm2 gangliosidosis, chronic idiopathic sensory neuropathy, chronic inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, chronic pain, chronic paroxysmal hemicrania, chronic sclerosing panencephalitis, chronic traumatic encephalopathy, chronobiological disorders, circadian rhythm disorder, circadian rhythm disorders, Claude's syndrome, clonic seizures, cluster headache, cocaine addiction, cocaine withdrawal, cocaine-related disorders, Cockayne's syndrome, colloid cysts of the third ventricle, colorado tick fever, coma, communicating hydrocephalus, communication disorders, complex partial seizures, compression neuropathy, compulsive buying disorder, conceptual apraxia, conduct disorders, conduction aphasia, conduction apraxia, congenital analgesia, congenital cytomegalovirus disease, congenital hydrocephalus, congenital hypothyroidism, congenital muscular dystrophy, congenital myasthenia, congenital myotonic dystrophy, congenital rubella syndrome, congophilic angiopathy, constipation, coprophilia, cornelia de lange syndrome, cortical dementias, cortical heteropias, corticobasal degeneration, corticobasal ganglionic degeneration, coxsackievirus, cranial meningoceles, craniopharyngioma, craniorachischisis, craniosynostosis, cranium bifidum, cretinism, Creutzfeldt-Jaknock outb disease, Cri-du-Chat syndrome, cruciate hemiplegia, cryptococcal granulomas, cryptococcosis, culturally related syndromes, culturally stereotyped reactions to extreme environmental conditions (arctic hysteria), Cushing syndrome, cyclothymia, cysticercosis, cytomegalovirus, Dandy-Walker malformation, deafness, defects in the metabolism of amino acids, dehydration, Dejerine-Roussy syndrome, Dejerine-Sottas disease, delayed and advanced sleep phase syndromes, delayed ejaculation, delayed puberty, delayed-sleep-phase syndrome, delerium due to alcohol, delerium due to intoxication, delerium due to withdrawal, delirium, dementia, and amnestic and other cognitive disorders,

delusional disorder, delusional disorder: erotomania subtype, delusional disorder: grandiose subtype, delusional disorder: jealousy subtype, delusional misidentification syndromes, dementia due to HIV disease, dementia pugilistica, dementias, dementias associated with extrapyramidal syndrome, dentatorubral-pallidoluyisian atrophy, dependent personality disorder, depersonalization disorder, depression, depressive personality disorder, dermoids, developmental speech and language disorder, devic syndrome, devivo disease, diabetes, diabetes insipidus, diabetic neuropathy, dialysis demential, dialysis dysequilibrium syndrome, diencephalic dementias, diencephalic dysfunction, diencephalic syndrome of infancy, diencephalic vascular dementia, diffuse sclerosis, digestive disorders, diphtheria, diplopia, disarthria, disassociation apraxia, disorders of carbohydrate metabolism, disorders of excessive somnolence, disorders of metal metabolism, disorders of purine metabolism, disorders of sexual arousal, disorders of sexual aversion, disorders of sexual desire, disorders of the sleep-wake schedule, dissociative disorders, dorsolateral tegmental pontine syndrome, Down syndrome, Down syndrome with dementia, drug dependance, drug overdose, drug-induced myasthenia, Duchenne muscular dystrophy, dwarfism, dysarthria, dysdiadochokinesia, dysembryoplastic neuroepithelial tumor, dysexecutive syndrome, dysgraphia, dyskinesia, dyskinetic cerebral palsy, dyslexia, dysmetria, dysomnia, dysosmia, dyspareunia, dysphagia, dysphasia, dysphonia, dysplasia, dyspnea, dysprosody, dyssomnia, dyssynergia, dyesthesia, dysthymia, dystonia, dystrophinopathies, early adolescent gender identity disorder, early infantile epileptic encephalopathy (Ohtahara syndrome, early myoclonic epileptic encephalopathy, Eaton-Lambert syndrome, echinococcus (hydatid cysts), echolalia, echovirus, eclampsia, Edward's syndrome, elimination disorders, embolismintracerebral hemorrhage, Emery-Dreifuss muscular dystrophy, encephalitis lethargica, encephaloceles, encephalotrigeminal angiomas, enophthalmos, enterovirus, enuresis, eosinophilic meningitis, ependymoma, epidural spinal cord compression, epilepsy, episodic ataxia, epstein-barr, equine encephalomyelitis, erectile dysfunction, essential thrombocythemia, essential tremor, esthesioneuroblastoma, excessive daytime somnolence, excessive secretion of antidiuretic hormone, excessive sleepiness, exhibitionism, expressive language disorder, extramedullary tumors, extrasylvian aphasias, extratemporal neocortical epilepsy,

fabry's disease, facioscapulohumeral muscular dystrophy, factitious disorder, factitious disorders, false memories, familial dysautonomia, familial periodic paralysis, familial spastic paraparesis, familial spastic paraplegias, fear disorders, feeding and eating disorders of infancy or early childhood, female sexual arousal disorder, fetal alcohol syndrome, fetishism, flaccid dysarthria, floppy infant syndrome, focal inflammatory demyelinating lesions with mass effect, focal neonatal hypotonia, folie à deux, foramen magnum tumors, Foville's syndrome, fragile-x syndrome, Freidrich 's ataxia, Frolich syndrome, frontal alexia, frontal convexity syndrome, frontotemporal dementia, frontotemporal dementias, frotteurism, fungal infection, galactocerebroside lipidosis, galactorrhea, ganglioneuroma, Gaucher disease, gaze palsy, gender identity disorder, generalized anxiety disorder, genital shrinking syndrome (Knock out, Suo-Yang), germ cell tumors, Gerstmann's syndrome, Gerstmann-Straüssler syndrome, Gerstmann-Straussler-Schenker disease, Gertmann's syndrome, gestational substance abuse syndromes, giant axonal neuropathy, gigantism, Gilles de la Tourette syndrome, glioblastoma multiforme, gliomas, gliomatosis cerebri, global aphasia, glossopharyngeal neuralgia, glycogen storage diseases, gm1-gangliosidosis, gm2-gangliosidosis, granular cell tumor, granulocytic brain edema, granulomas, granulomatous angiitis of the brain, Grave's disease, growild typeh hormone deficit , growild typeh-hormone secreting adenomas, guam-Parkinson complex dementia, Guillain-Barré syndrome, Hallervorden-Spatz disease, hallucinogen persisting perception disorder, hallucinogen related disorders, hartnup disease, headache, helminthic infections (trichinellosis), hemangioblastomas, hemangiopericytomas, hemiachromatopsia, hemianesthesia, hemianopsia, hemiballism, hemiballismus, hemihypacusis, hemihypesthesia, hemiparesis, hemispatial neglect, hemophilus influenza meningitis, hemorrhagic cerebrovascular disease, hepatic coma, hepatic encephalopathy, hepatolenticular degeneration (Wilson disease), hereditary amyloid neuropathy, hereditary ataxias, hereditary cerebellar ataxia, hereditary neuropathies, hereditary nonprogressive chorea, hereditary predisposition to pressure palsies, hereditary sensory autonomic neuropathy, hereditary sensory neuropathy, hereditary spastic paraplegia, hereditary tyrosinemia, heremichorea, hermifacial spasm, herniation syndromes, herpes encephalitis, herpes infections, herpes zoster, herpres simplex, heterotopia, hexacarbon neuropathy,

histrionic personality disorder, HIV, Holmes-Adie syndrome, homonymous quadrantanopsia, Horner's syndrome, human β -mannosidosis, Hunter's syndrome, Huntington's chorea, Huntington's disease, Hurler's syndrome, Hwa-Byung, hydraencephaly, hydrocephalus, hyper thyroidism, hyperacusis, hyperalgesia, hyperammonemia, hypereosinophilic syndrome, hyperglycemia, hyperkalemic periodic paralysis, hyperkinesia, hyperkinesis, hyperkinetic dysarthria, hyperosmia, hyperosmolar hyperglycemic nonketonic diabetic coma, hyperparathyroidism, hyperphagia, hyperpituitarism, hyperprolactinemia, hypersexuality, hypersomnia, hypersomnia secondary to drug intake, hypersomnia-sleep-apnea syndrome, hypersomnolence, hypertension, hypertensive encephalopathy, hyperthermia, hyperthyroidism (Graves disease), hypertonia, hypnagogic (predormital) hallucinations, hypnogenic paroxysmal dystonia, hypoadrenalism, hypoalgesia, hypochondriasis, hypoglycemia, hypoinsulinism, hypokalemic periodic paralysis, hypokinesia, hypokinetic dysarthria, hypomania, hypoparathyroidism, hypophagia, hypopituitarism, hypoplasia, hyposmia, hyposthenuria, hypotension, hypothermia, hypothyroid neuropathy, hypothyroidism, hypotonia, Hyrler syndrome, hysteria, ideational apraxia, ideomotor apraxia, idiopathic hypersomnia, idiopathic intracranial hypertension, idiopathic orthostatic hypotension, immune mediated neuropathies, impersistence, impotence, impulse control disorders, impulse dyscontrol and aggression syndromes, impulse-control disorders, incontinence, incontinentia pigmenti, infantile encephalopathy with cherry-red spots, infantile neuraxonal dystrophy, infantile spasms, infantilism, infarction, infertility, influenza, inhalant related disorders, insomnias, insufficient sleep syndrome, intention tremor, intermittent explosive disorder, internuclear ophthalmoplegia, interstitial (hydrocephalic) edema, intoxication, intracranial epidural abscess, intracranial hemorrhage, intracranial hypotension, intracranial tumors, intracranial venous-sinus thrombosis, intradural hematoma, intramedullary tumors, intravascular lymphoma, ischemia, ischemic brain edema, ischemic cerebrovascular disease, ischemic neuropathies, isolated inflammatory demyelinating CNS syndromes, Jackson-Collet syndrome, Jakob outb-Creutzfeld disease, Japanese encephalitis, jet lag syndrome, Joseph disease, Joubert's syndrome, juvenile neuroaxonal dystrophy, Kayak-Svimmel, Kearns-Sayre syndrome, kinky hair disease (Menkes syndrome), Kleine-Levin

syndrome, kleptomania, Klinefelter's syndrome, Kluver-Bucy syndrome, Knock
 outerber-Salus-Elschnig syndrome, Knock outtsaknock outff's syndrome, krabbe
 disease, krabbe leuknock outdystrophy, Kugelberg-Welander syndrome, kuru, Lafora's
 disease, language deficits, language related disorders, latah-type reactions, lateral mass
 herniation syndrome, lateropulsation, lathyrism, Laurence-Moon Biedl syndrome,
 Laurence-Moon syndrome, lead poisoning, learning disorders, leber hereditary optic
 atrophy, left ear extinction, legionella pneumophilia infection, Leigh's disease, Lennoc-
 Gastaut syndrome, Lennox-Gastaut's syndrome, leprosy, leptospirosis, Lesch-Nyhan
 syndrome, leukemia, leuknock outdystrophies, Lévy-Roussy syndrome, lewy body
 dementia, lewy body disease, limb girdle muscular dystrophies, limbic encephalitis,
 limbic encephalopathy, lissencephaly, localized hypertrophic neuropathy, locked-in
 syndrome, logoclonia, low pressure headache, Lowe syndrome, lumbar tumors, lupus
 anticoagulants, lyme disease, lyme neuropathy, lymphocytic choriomeningitis,
 lymphomas, lysosomal and other storage diseases, macroglobinemia, major depression
 with melancholia, major depression with psychotic features, major depression without
 melancholia, major depressive (unipolar) disorder, male orgasmic disorder,
 malformations of septum pellucidum, malignant peripheral nerve sheath tumors,
 malingers, mania, mania with psychotic features, mania without psychotic features,
 maple syrup urine disease, Marchiafava-Bignami syndrome, Marcus Gunn syndrome,
 Marie-Foix syndrome, Marinesco-Sjögren syndrome, Maroteaux-Lamy syndrome,
 masochism, masturbatory pain, measles, medial frontal syndrome, medial medullary
 syndrome, medial tegmental syndrome, medication-induced movement disorders,
 medullary dysfunction, medulloblastomas, medulloepithelioma, megalencephaly,
 melanocytic neoplasms, memory disorders, memory disturbances, meniere syndrome,
 meningeal carcinomatosis, meningeal sarcoma, meningial gliomatosis, meningiomas,
 meningism, meningitis, meningococcal meningitis, mental neuropathy (the numb chin
 syndrome), mental retardation, mercury poisoning, metabolic neuropathies,
 metachromatic leuknock outdystrophy, metastatic neuropathy, metastatic tumors,
 metazoal infections, microcephaly, microencephaly, micropolygyria, midbrain
 dysfunction, midline syndrome, migraine, mild depression, Millard-Gubler syndrome,
 Miller-Dieker syndrome, minimal brain dysfunction syndrome, miosis, mitochondrial

encephalopathy with lactic acidosis and stroke (melas), mixed disorders of scholastic skills, mixed dysarthrias, mixed transcortical aphasia, Möbius syndrome, Mollaret meningitis, monoclonal gammopathy, mononeuritis multiplex, monosymptomatic hypochondriacal psychosis, mood disorders, Moritz Benedikt syndrome, Morquio syndrome, Morton's neuroma, motor neuron disease, motor neurone disease with dementia, motor neuropathy with multifocal conduction block, motor skills disorder, mucopolidoses, mucopolysaccharide disorders, mucopolysaccharidoses, multifocal eosinophilic granuloma, multiple endocrine adenomatosis, multiple myeloma, multiple sclerosis, multiple system atrophy, multiple systems atrophy, multisystemic degeneration with dementia, mumps, Munchausen syndrome, Munchausen syndrome by proxy, muscular hypertonia, mutism, myasthenia gravis, mycoplasma pneumoniae infection, myoclonic seizures, myoclonic-astatic epilepsy (doose syndrome), myoclonus, myotonia congenita, myotonic dystrophy, myotonic muscular dystrophy, nacoletsy, narcissistic personality disorder, narcolepsy, narcolepsy-cataplexy syndrome, necrophilia, nectrotizing encephalomyelopathy, Nelson's syndrome, neocerebellar syndrome, neonatal myasthenia, neonatal seizures, nervios, nerves, neurasthenia, neuroacanthocytosis, neuroaxonal dystrophy, neurocutaneous disorders, neurofibroma, neurofibromatosis, neurogenic orthostatic hypotension, neuroleptic malignant syndrome, neurologic complications of renal transplantation, neuromyelitis optica, neuromyotonia (Isaacs syndrome), neuronal ceroid lipofuscinoses, neuro-ophthalmic disorders, neuropathic pain, neuropathies associated with infections, neuropathy associated with cryoglobulins, neuropathy associated with hepatic diseases, neuropathy induced by cold, neuropathy produced by chemicals, neuropathy produced by metals, neurosyphilis, new variant Creutzfeldt-Jakob disease, nicotine dependence, nicotine related disorders, nicotine withdrawal, niemann-pick disease, nocturnal dissociative disorders, nocturnal enuresis, nocturnal myoclonus, nocturnal sleep-related eating disorders, noecerebellar syndrome, non-alzheimer frontal-lobe degeneration, nonamyloid polyneuropathies associated with plasma cell dyscrasia, non-lethal suicidal behavior, nonlocalizing aphasic syndromes, normal pressure hydrocephalus, Nothnagel's syndrome, nystagmus, obesity, obsessive-compulsive (anankastic) personality disorder, obsessive-compulsive disorder, obstetric factitious disorder, obstructive hydrocephalus,

obstructive sleep apnea, obstructive sleep apnoea syndrome, obstructive sleep hypopnoea syndrome, occipital dementia, occlusive cerebrovascular disease, oculocerebrorenal syndrome of lowe, oculomotor nerve palsy, oculopharyngeal muscular dystrophy, oligodendrogliomas, olivopontocerebellar atrophy, ondine's curse, one and a half syndrome, onychophagia, opiate dependance, opiate overdose, opiate withdrawal, opioid related disorders, oppositional defiant disorder, opsoclonus, orbitofrontal syndrome, orgasmic anhedonia, orgasmic disorders, osteosclerotic myeloma, other disorders of infancy, childhood, or adolescence, other medication-induced movement disorders, pachygyria, paedophilia, pain, pain syndromes, painful legs-moving toes syndrome, paleocerebellar syndrome, palilalia, panhypopituitarism, panic disorder, panic disorders, papillomas of the choroid plexus, paraganglioma, paragonimiasis, paralysis, paralysis agitans (shaking palsy), paramyotonia congenita, paraneoplastic cerebellar degeneration, paraneoplastic cerebellar syndrome, paraneoplastic neuropathy, paraneoplastic syndromes, paranoia, paranoid personality disorder, paranoid psychosis, paraphasia, paraphilias, paraphrenia, parasitic infections, parasomnia, parasomnia overlap disorder, parenchymatous cerebellar degeneration, paresis, paresthesia, parinaud's syndrome, Parkinson's disease, Parkinson-dementia complex of guam, Parkinsonism, Parkinsonism-plus syndromes, Parkinson's disease, paroxysmal ataxia, paroxysmal dyskinesia, partial (focal) seizures, partialism, passive-aggressive (negativistic) personality disorder, Patau's syndrome, pathological gambling, peduncular hallucinosis, Pelizaeus-Merzbacher disease, perineurioma, peripheral neuropathy, perisylvian syndromes, periventricular leukoencephalomalacia, periventricular white matter disorder, periventricular-intraventricular hemorrhage, pernicious anemia, peroneal muscular atrophy, peroxisomal diseases, perseveration, persistence of cavum septi pellucidi, persistent vegetative state, personality disorders, pervasive developmental disorders, phencyclidine (or phencyclidine-like) related disorders, phencyclidine delirium, phencyclidine psychosis, phencyclidine-induced psychotic disorder, phenylketonuria, phobic anxiety disorder, phonic tics, photoreceptor degeneration, pibloktoq, Pick's disease, pineal cell tumors, pineoblastoma, pineocytoma, pituitary adenoma, pituitary apoplexy, pituitary carcinoma, pituitary dwarfism, placebo effect, Plummer's disease, pneumococcal meningitis, poikilothermia, polio,

polycythemia vera, polydipsia, polyglucosan storage diseases, polymicrogyria, polymyositis, polyneuropathy with dietary deficiency states, polysubstance related disorder, polyuria, pontine dysfunction, pontosubicular neuronal necrosis, porencephaly, porphyric neuropathy, portal-systemic encephalopathy, postcoital headaches, postconcussion syndrome, postencephalic Parkinson syndrome, posthemorrhagic hydrocephalus, postinflammatory hydrocephalus, postpartum depression, postpartum psychoses, postpolio syndrome, postpsychotic depression, post-stroke hypersomnia, post-traumatic amnesia, post-traumatic epilepsy, post-traumatic hypersomnia, post-traumatic movement disorders, post-traumatic stress disorder, post-traumatic syndromes, Prader-Willi syndrome, precocious puberty, prefrontal dorsolateral syndrome, prefrontal lobe syndrome, premenstrual stress disorder, premenstrual syndrome, primary amebic meningoencephalitis, primary CNS lymphoma, primary idiopathic thrombosis, primary lateral sclerosis, primitive neuroectodermal tumors, prion disease, problems related to abuse or neglect, progressive bulbar palsy, progressive frontal lobe dementias, progressive multifocal lueknock outencephalopathy, progressive muscular atrophy, progressive muscular dystrophies, progressive myoclonic epilepsies, progressive myoclonus epilepsies, progressive non-fluent aphasia, progressive partial epilepsies, progressive rubella encephalitis, progressive sclerosing poliodystrophy (Alpers disease), progressive subcortical gliosis, progressive supranuclear palsy, progressive supranuclear paralysis, progrssive external ophthalmoplegia, prolactinemia , prolactin-secreting adenomas, prosopagnosia, protozoan infection, pseudobulbar palsy, pseudocyesis, pseudodementia, psychic blindness, psychogenic excoriation, psychogenic fugue, psychogenic pain syndromes, psychological mutism, psychosis after brain injury, psychotic syndromes, ptosis, public masturbation, puerperal panic, pulmonary edema, pure word deafness, pyromania, quadrantanopsia, rabies; radiation neuropathy, Ramsay Hunt syndrome, rape traume syndrome, rapid cycling disorder, rapid ejaculation, Raymond-Cestan-Chenais syndrome, receptive language disorder, recovered memories, recurrent bipolar episodes, recurrent brief dpression, recurrent hypersomnia, recurrent major depression, refsum disease, reiterative speech disturbances, relational problems, rem sleep behavior disorder, rem sleep behavioral disorder, repetitive self-mutilation, repressed memories, respiratory dysrhythmia, restless legs syndrome, Rett's syndrome,

Reye syndrome, rhythmic movement disorders, rocky mountain spotted fever, rostral basal pontine syndrome, rubella, Rubinstein-Taybi syndrome, sadistic personality disorder, salla disease, Sandhoff disease, Sanfilippo syndrome, sarcoid neuropathy, sarcoidosis, scapuloperoneal syndromes, schistosomiasis (bilharziasis), schizencephaly, schizoaffective disorder, schizoid personality disorder, schizophrenia, schizophrenia and other psychotic disorders, schizophrenia-like psychosis, schizophreniform disorder, schizotypal personality disorder, school-refusal anxiety disorder, schwannoma, scrub typhus, seasonal depression, secondary spinal muscular atrophy, secondary thrombosis, sedative hypnotic or anxiolytic-related disorders, seizure disorders, selective mutism, self-defeating (masochistic) personality disorder, semen-loss syndrome (shen-k'uei, dhat, jiryan, sukra prameha), senile chorea, senile dementia, sensory perineuritis, separation anxiety disorder, septal syndrome, septo-optic dysplasia, severe hypoxia, severe myoclonic epilepsy, sexual and gender identity disorders, sexual disorders, sexual dysfunctions, sexual pain disorders, sexual sadism, Shapiro syndrome, shift work sleep disorder, Shy-Drager syndrome, sialidosis, sialidosis type 1, sibling rivalry disorder, sickle cell anemia, Simmonds disease, simple partial seizures, simultanagnosia, sleep disorders, sleep paralysis, sleep terrors, sleep-related enuresis, sleep-related gastroesophageal reflux syndrome, sleep-related headaches, sleep-wake disorders, sleepwalking, Smith-Magenis syndrome, social anxiety disorder, social phobia, social relationship syndromes, somatoform disorders, somnambulism, Sotos syndrome, spasmodic dysphonia, spasmodic torticollis (wry neck), spastic cerebral palsy, spastic dysarthria, specific developmental disorder of motor function, specific developmental disorders of scholastic skills, specific developmental expressive language disorder, specific developmental receptive language disorder, specific disorders of arithmetical skills, specific phobia, specific speech articulation disorder, specific spelling disorder, speech impairment, spina bifida, spinal epidural abcess, spinal muscular atrophies, spinocerebellar ataxias, spirochete infections, spongiform encephalopathies, spongy degeneration of the nervous system, St. Louis encephalitis, stammer, staphylococcal meningitis, startle syndromes, status marmoratus, steele-richardson-olszewski syndrome, stereotypic movement disorder, stereotypies, stiff-man syndrome, stiff-person syndrome, stimulant psychosis, Strachan syndrome (nutritional neuropathy), streptococcal

meningitis, striatonigral degeneration, stroke, strongyloidiasis, sturge-weber disease (Krabbe-Weber-Dimitri disease), stutter, subacute combined degeneration of the spinal cord, subacute motor neuronopathy, subacute necrotic myelopathy, subacute sclerosing panencephalitis, subacute sensory neuronopathy, subarachnoid hemorrhage, subcortical aphasia, subfalcine herniation syndrome, substance abuse, substance related disorders, sudanophilic leukoencephalopathy, sudden infant death syndrome, suicide, sulfatide lipidosis, susto, espanto, meido, sydenham chorea, symmetric neuropathy associated with carcinoma, sympathotonic orthostatic hypotension, syncope, syndromes related to a cultural emphasis on learnt dissociation, syndromes related to a cultural emphasis on presenting a physical appearance pleasing to others (taijin-kyofu reactions), syndromes related to acculturative stress, syringobulbia, syringomyelia, systemic lupus erythematosus, tachycardia, tachypnea, Tangier disease, tardive dyskinesia, Tay-sachs disease, telangiectasia, telencephalic leukoencephalopathy, telephone scatologia, temporal lobe epilepsy, temporoparietal dementia, tension-type headache, teratomas, tetanus, tetany, thalamic syndrome, thallium poisoning, thoracic tumors, thrombotic thrombocytopenic purpura, thyroid disorders, tic disorders, tick paralysis, tick-borne encephalitis, tinnitus, toxic neuropathy, tonic seizures, tonic-clonic seizures, torticollis, Tourette syndrome, toxic neuropathies, toxoplasmosis, transcortical motor aphasia, transcortical sensory aphasia, transient epileptic amnesia, transient global amnesia, transitional sclerosis, transvestic fetishism, traumatic brain injury, traumatic neuroma, traumatic mutism, tremors, trichinosis, trichotillomania, trigeminal neuralgia, trochlear nerve palsy, tropical ataxic neuropathy, tropical spastic paraparesis, trypanosomiasis, tuberculomas, tuberculous meningitis, tuberous sclerosis, tumors, Turner's syndrome, typhus fever, ulegyria, unciniate fits, Unverricht-Lundborg's disease, upper airway resistance syndrome, upward transtentorial herniation syndrome, uremic encephalopathy, uremic neuropathy, urophilia, vaccinia, varicella-zoster, vascular dementia, vascular malformations, vasculitic neuropathies, vasogenic edema, velocardiofacial syndrome, venous malformations, ventilatory arrest, vertigo, vincristine toxicity, viral infections, visuospatial impairment, Vogt-Knock outyanagi-Harada syndrome, Von Hippel-Lindau disease, Von Racklinghausen disease, voyeurism, Waldenström's macroglobulinemia, Walker-Warburg syndrome, Wallenburg's

syndrome, Walleyed syndrome, Weber's syndrome, Wernicke's encephalopathy, Werdnig-Hoffmann disease, Wernicke's encephalopathy, Wernicke-Knorr syndrome, Wernicke's aphasia, West's syndrome, Whipple disease, Williams syndrome, Wilson disease, Windigo, Witkop's syndrome, Witkop's syndrome, withdrawal with grand mal seizures, withdrawal with perceptual disturbances, withdrawal without complications, Wolman disease, xeroderma pigmentosum, xyy syndrome, Zellweger syndrome.

398. The method of any of claims 37-42, 181-183, and 253-258, wherein said neurological disease or disorder involves one or more tissues selected from the group consisting of hypothalamus, amygdala, pituitary, nervous system, brainstem, cerebellum, cortex, frontal cortex, hippocampus, striatum, and thalamus.

399. The method of any of claims 43-48, 184-186, and 259-264, wherein said disease or disorder of the adrenal gland is selected from the group consisting of 11-hydroxylase deficiency, 17-hydroxylase deficiency, 3 β -dehydrogenase deficiency, acquired immune deficiency syndrome, ACTH-dependent adrenal hyperfunction (Cushing disease), ACTH-independent adrenal hyperfunction, acute adrenal insufficiency, adrenal abscess, adrenal adenoma, adrenal calcification, adrenal cysts, adrenal cytomegaly, adrenal dysfunction in glycerol kinase deficiency, adrenal hematoma, adrenal hemorrhage, adrenal histoplasmosis, adrenal hyperfunction, adrenal hyperplasia, adrenal medullary hyperplasia, adrenal myelolipoma, adrenal tuberculosis, adrenocortical adenoma, adrenocortical adenoma with primary hyperaldosteronism (Conn's syndrome), adrenocortical carcinoma, adrenocortical carcinoma with Cushing's syndrome, adrenocortical hyperfunction, adrenocortical insufficiency, adrenocortical neoplasms, adrenoleukodystrophy, amyloidosis, anencephaly, autoimmune Addison's disease, Beckwith-Wiedemann syndrome, bilateral adrenal hyperplasia, chronic insufficiency of adrenocortical hormone synthesis, complete 21-hydroxylase deficiency, congenital adrenal hyperplasia, congenital adrenal hypoplasia, cortical hyperplasia, desmolase deficiency, ectopic ACTH syndrome, excess aldosterone secretion, excess cortisol secretion (Cushing's syndrome), excess secretion of adrenocortical hormones, excess sex hormone secretion, familial glucocorticoid

deficiency, functional "black" adenomas, ganglioneuroblastoma, ganglioneuroma, glucocorticoid remediable hyperaldosteronism, herpetic adrenalitis, hyperaldosteronism, idiopathic Addison's disease, idiopathic hyperaldosteronism with bilateral hyperplasia of zona glomerulosa, iatrogenic hypercortisolism, lysosomal storage diseases, macronodular hyperplasia, macronodular hyperplasia with marked adrenal enlargement, malignant lymphoma, malignant melanoma, metastatic carcinoma, metastatic tumors, micronodular hyperplasia, multiple endocrine neoplasia syndromes, multiple endocrine neoplasia type 1 (Wermer syndrome), multiple endocrine neoplasia type 2a (Sipple syndrome), multiple endocrine neoplasia type 2b, neuroblastoma, Niemann-Pick disease, ovarian thecal metaplasia, paraganglioma, partial 21-hydroxylase deficiency, pheochromocytoma, primary aldosteronism (Conn's syndrome), primary chronic adrenal insufficiency (Addison's disease), primary hyperaldosteronism, primary mesenchymal tumors, primary pigmented nodular adrenocortical disease, salt-wasting congenital adrenal hyperplasia, secondary Addison's disease, secondary hyperaldosteronism, selective hypoaldosteronism, simple virilizing congenital adrenal hyperplasia, Waterhouse-Friderichsen syndrome, and Wolman's disease.

400. The method of any of claims 49-54, 187-189, and 265-270, wherein said disease or disorder of the colon is selected from the group consisting of acute self-limited infectious colitis, adenocarcinoma, adenoma, adenoma-carcinoma sequence, adenomatous polyposis coli, adenosquamous carcinomas, allergic (eosinophilic) proctitis and colitis, amebiasis, amyloidosis, angiodysplasia, anorectal malformations, blue rubber bleb nevus syndrome, brown bowel syndrome, Campylobacter fetus infection, carcinoid tumors, carcinoma of the anal canal, carcinoma of the colon and rectum, chlamydial proctitis, Crohn's disease, clear cell carcinomas, Clostridium difficile pseudomembranous enterocolitis, collagenous colitis, colonic adenoma, colonic diverticulosis, colonic inertia, colonic ischemia, congenital atresia, congenital megacolon (Hirschsprung's disease), congenital stenosis, constipation, Cowden's syndrome, cystic fibrosis, cytomegalovirus colitis, diarrhea, dieulafor lesion, diversion colitis, diverticulitis, diverticulosis, drug-induced diseases, dysplasia and malignancy in inflammatory bowel disease, Ehlers-Danlos syndromes, enterobiasis, familial

adenomatous polyposis, familial polyposis syndromes, Gardner's syndrome, gastrointestinal stromal neoplasms, hemangiomas and vascular anomalies, hemorrhoids, hereditary hemorrhagic telangiectasia, herpes colitis, hyperplastic polyps, idiopathic inflammatory bowel disease, incontinence, inflammatory bowel syndrome, inflammatory polyps, inherited adenomatous polyposis syndromes, intestinal hamartomas, intestinal pseudo-obstruction, irritable bowel syndrome, ischemic colitis, juvenile polyposis, juvenile polyps, Klippel-Trénaunay-Weber syndrome, leiomyomas, lipomas, lymphocytic (microscopic) colitis, lymphoid hyperplasia and lymphoma, malaknock outplakia, malignant lymphoma, malignant neoplasms, malrotation, metastatic neoplasms, mixed hyperplastic and adenomatous polyps, mucosal prolapse syndrome, neonatal necrotizing enterocolitis, neuroendocrine cell tumors, neurogenic tumors, neutropenic enterocolitis, non-neoplastic polyps, Peutz-Jeghers syndrome, pneumatosis cystoides intestinalis, polyposis coli, pseudomembranous colitis, pseudoxanthoma elasticum, pure squamous carcinomas, radiation colitis, schistosomiasis, Shigella colitis (bacillary dysentery), spindle cell carcinomas, spirochetosis, stercoral ulcers, stromal tumors, systemic sclerosis and CREST syndrome, trichuriasis, tubular adenoma (adenomatous polyp, polypoid adenoma), Turcot's syndrome, Turner's syndrome, ulcerative colitis, villous adenoma, and volvulus.

401. The method of any of claims 55-60, 190-192, and 271-276, wherein said cardiovascular disease or disorder is selected from the group consisting of acute coronary syndrome, acute idiopathic pericarditis, acute rheumatic fever, American trypanosomiasis (Chagas' disease), angina pectoris, ankylosing spondylitis, anomalous pulmonary venous connection, anomalous pulmonary venous drainage, aortic atresia, aortic regurgitation, aortic stenosis, aortic valve insufficiency, aortopulmonary septal defect, asymmetric septal hypertrophy, asystole, atrial fibrillation, atrial flutter, atrial septal defect, atrioventricular septal defect, autoimmune myocarditis, bacterial endocarditis, calcific aortic stenosis, calcification of the aortic valve, calcification of the valve ring, carcinoid heart disease, cardiac amyloidosis, cardiac arrhythmia, cardiac failure, cardiac myxoma, cardiac rejection, cardiac tamponade, cardiogenic shock, cardiomyopathy of pregnancy, chronic adhesive pericarditis, chronic constrictive

pericarditis, chronic left ventricular failure, coarctation of the aorta, complete heart block, complete transposition of the great vessels, congenital bicuspid aortic valves, congenital narrowing of the left ventricular outflow tract, congenital pulmonary valve stenosis, congenitally corrected transposition of the great arteries, congestive heart failure, constrictive pericarditis, cor pulmonale, coronary artery origin from pulmonary artery, coronary atherosclerosis, dilated (congestive) cardiomyopathy, diphtheria, double inlet left ventricle, double outlet right ventricle, Ebstein's malformation, endocardial fibroelastosis, endocarditis, endomyocardial fibrosis, eosinophilic endomyocardial disease (Löffler endocarditis), fibroma, glycogen storage diseases, hemochromatosis, hypertensive heart disease, hyperthyroid heart disease, hypertrophic cardiomyopathy, hypothyroid heart disease, idiopathic dilated cardiomyopathy, idiopathic myocarditis, infectious myocarditis, infective endocarditis, ischemic heart disease, left ventricular failure, Libman-Sachs endocarditis, lupus erythematosus, Lyme disease, marantic endocarditis, metastatic tumors, mitral insufficiency, mitral regurgitation, mitral stenosis, mitral valve prolapse, mucopolysaccharidoses, multifocal atrial tachycardia, myocardial infarction, myocardial ischemia, myocardial rupture, myocarditis, myxomatous degeneration, nonatheromatous coronary artery disease, nonbacterial thrombotic endocarditis, noninfectious acute pericarditis, nonviral infectious pericarditis, obliterative cardiomyopathy, patent ductus arteriosus, pericardial effusion, pericardial tumors, pericarditis, persistent truncus arteriosus, premature ventricular contraction, progressive infarction, pulmonary atresia with intact ventricular septum, pulmonary atresia with ventricular septal defect, pulmonary insufficiency, pulmonary regurgitation, pulmonary stenosis, pulmonary valve lesions, pulmonary valve stenosis, pyogenic pericarditis, Q fever, radiation myocarditis, restrictive cardiomyopathy, rhabdomyoma, rheumatic aortic stenosis, rheumatic heart disease, Rocky Mountain spotted fever, rupture of the aortic valve, sarcoid myocarditis, scleroderma, sphingolipidoses, sinus brachycardia, sudden death, syphilis, systemic embolism from mural thrombi, systemic lupus erythematosus, tetralogy of Fallot, thiamine deficiency (Beriberi) heart disease, thoracic outlet syndrome, Torsade de Pointes, toxic cardiomyopathy, toxic myocarditis, toxoplasmosis, trichinosis, tricuspid atresia, tricuspid insufficiency, tricuspid regurgitation, tricuspid stenosis, tricuspid valve lesions, tuberculous pericarditis, typhus,

ventricular aneurysm, ventricular fibrillation, ventricular septal defect, ventricular tachycardia, ventriculoarterial septal defect, viral pericarditis, and Wolff-Parkinson-White syndrome.

402. The method of any of claims 61-66, 193-195, and 277-282, wherein said disease or disorder of the intestine is selected from the group consisting of abdominal hernia, abetalipoproteinemia, abnormal rotation, acute hypotensive hypoperfusion, acute intestinal ischemia, acute small intestinal infarction, adenocarcinoma, adenoma, adhesions, amebiasis, anemia, arterial occlusion, atypical mycobacteriosis, bacterial diarrhea, bacterial overgrowth syndromes, botulism, *Campylobacter fetus* infection, *Campylobacter jejuni*, carbohydrate absorption defects, carcinoid tumors, celiac disease (nontropical sprue, gluten-induced enteropathy), cholera, Crohn's disease, chronic intestinal ischemia, *Clostridium difficile* pseudomembranous enterocolitis, *Clostridium perfringens*, congenital umbilical hernia, Cronkhite-Canada syndrome, cytomegalovirus enterocolitis, diarrhea, diarrhea caused by invasive bacteria, diverticulitis, diverticulosis, dysentery, enteroinvasive and enterohemorrhagic *Escherichia coli* infection, eosinophilic gastroenteritis, failure of peristalsis, familial polyposis syndromes, food poisoning, fungal enteritis, gangliocytic paragangliomas, Gardner's syndrome, gastrointestinal stromal neoplasms, giardiasis, hemorrhoids, hernia, hyperplastic polyps, idiopathic inflammatory bowel disease, ileus, imperforate anus, intestinal (abdominal) ischemia, intestinal atresia, intestinal cryptosporidiosis, microsporidiosis & isosporiasis in AIDS, intestinal hamartomas, intestinal helminthiasis, intestinal hemorrhage, intestinal infiltrative disorders, intestinal lymphangiectasia, intestinal obstruction, intestinal perforation, intestinal reduplication, intestinal stenosis, intestinal tuberculosis, intussusception, jejunal diverticulosis, juvenile polyposis, juvenile retention polyps, lactase deficiency, lymphomas, malabsorption syndrome, malignant lymphoma, malignant neoplasms, malrotations, mechanical obstruction, Meckel's diverticulum, meconium ileus, mediterranean lymphoma, mesenchymal tumors, mesenteric vasculitis, mesenteric vein thrombosis, metastatic neoplasms, microvillus inclusion disease, mixed hyperplastic and adenomatous polyps, neonatal necrotizing enterocolitis, nodular duodenum, nonocclusive intestinal ischemia,

nonspecific duodenitis, nontyphoidal salmonellosis, omphalocele, parasitic infections, peptic ulcer disease, Peutz-Jeghers syndrome, pneumatosis cystoides intestinalis, poorly differentiated neuroendocrine carcinomas, primary lymphoma, protein-losing enteropathy, Salmonella gastroenteritis, sarcoidosis, sarcomas, shigellosis, staphylococcal food poisoning, steatorrhea, sugar intolerance, thrombosis of the mesenteric veins, toxigenic diarrhea, toxigenic Escherichia coli infection, tropical sprue, tubular adenoma (adenomatous polyp, polypoid adenoma), typhoid fever, ulcers, vascular malformations, villous adenoma, viral enteritis, viral gastroenteritis, visceral myopathy, visceral neuropathy, vitelline duct remnants, volvulus, Western-type intestinal lymphoma, Whipple's disease (intestinal lipopystrophy), Yersinia enterocolitica & Yersinia pseudotuberculosis infection, and Zollinger-Ellison syndrome.

403. The method of any of claims 67-72, 196-198, and 283-288, wherein said disease or disorder of the kidney is selected from the group consisting of acquired cystic disease, acute (postinfectious) glomerulonephritis, acute infectious interstitial nephritis, acute interstitial nephritis, acute pyelonephritis, acute renal failure, acute transplant failure, acute tubular necrosis, adult polycystic kidney disease, AL amyloid, analgesic nephropathy, anti-glomerular basement membrane disease (Goodpasture's Syndrome), asymptomatic hematuria, asymptomatic proteinuria, autosomal dominant polycystic kidney disease, autosomal recessive polycystic kidney disease, Bence Jones cast nephropathy, benign familial hematuria, benign nephrosclerosis and atheromatous embolization, bilateral cortical necrosis, chronic glomerulonephritis, chronic interstitial nephritis, chronic pyelonephritis, chronic renal failure, chronic transplant failure, circulating immune complex nephritis, crescentic glomerulonephritis, cryoglobulinemia, cystic renal dysplasia, diabetic glomerulosclerosis, diabetic nephropathy, dialysis cystic disease, drug induced (allergic) acute interstitial nephritis, ectopic kidney, Fabry's disease, familial juvenile nephronophthisis-medullary cystic disease complex, focal glomerulosclerosis (segmental hyalinosis), glomerulocystic disease, glomerulonephritis, glomerulonephritis associated with bacterial endocarditis, glomerulosclerosis, hemolytic-uremic syndrome, Henoch-Schönlein purpura, hepatitis-associated glomerulonephritis, hereditary nephritis (Alport syndrome), horseshoe kidney,

hydronephrosis, IgA nephropathy, infantile polycystic kidney disease, ischemic acute tubular necrosis, light-chain deposit disease, malignant nephrosclerosis, medullary cystic disease, membranoproliferative (mesangiocapillary) glomerulonephritis, membranous glomerulonephritis, membranous nephropathy, mesangial proliferative glomerulonephritis (includes Berger's Disease), minimal change glomerular disease, minimal change nephrotic syndrome, nephritic syndrome, nephroblastoma (Wilms tumor), nephronophthisis (medullary cystic disease complex), nephrotic syndrome, plasma cell dyscrasias (monoclonal immunoglobulin-induced renal damage), polyarteritis nodosa, proteinuria, pyelonephritis, rapidly progressive (crescentic) glomerulonephritis, renal agenesis, renal amyloidosis, renal cell carcinoma, renal dysgenesis, renal dysplasia, renal hypoplasia, renal infection, renal osteodystrophy, renal stones (urolithiasis), renal tubular acidosis, renal vasculitis, renovascular hypertension, scleroderma (progressive systemic sclerosis), secondary acquired glomerulonephritis, simple renal cysts, systemic lupus erythematosus, thin basement membrane nephropathy, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, toxic acute tubular necrosis, tubular defects, tubulointerstitial disease in multiple myeloma, urate nephropathy, urinary obstruction, and vasculitis.

404. The method of any of claims 73-78, 199-201, and 289-294, wherein said disease or disorder of the liver is selected from the group consisting of acute alcoholic hepatitis (acute sclerosing hyaline necrosis of the liver), acute graft-versus-host disease, acute hepatitis, acute hepatocellular injury associated with infectious diseases other than viral hepatitis, acute liver failure, acute viral hepatitis, adenovirus hepatitis, Alagille syndrome, alcoholic cirrhosis, alcoholic hepatitis, alcoholic liver disease, alpha1-antitrypsin deficiency, amebic abscess, angiolipoma, angiosarcoma, ascending cholangitis, autoimmune chronic active hepatitis (lupoid hepatitis), bile duct adenoma, bile duct cystadenocarcinoma, bile duct cystadenoma, biliary atresia, biliary cirrhosis, biliary papillomatosis, bridging necrosis, Budd-Chiari syndrome, Byler disease, cardiac fibrosis of the liver, Caroli disease, cavernous hemangioma, cholangiocarcinoma, cholangitic abscess, cholestasis, cholestatic viral hepatitis, chronic active hepatitis, chronic alcoholic liver disease, chronic graft-versus-host disease, chronic hepatic venous

congestion, chronic hepatitis, chronic liver failure, chronic passive congestion, chronic viral hepatitis, cirrhosis, combined hepatocellular and cholangiocarcinoma, confluent hepatic necrosis, congenital hepatic fibrosis, Crigler-Najjar syndrome, cryptogenic cirrhosis, cystic fibrosis, defects of coagulation, delta hepatitis, Dubin-Johnson syndrome, epithelioid hemangioendothelioma, erythrohepatic protoporphyria, extrahepatic biliary obstruction (primary biliary cirrhosis), fatty change, fatty liver, focal necrosis, focal nodular hyperplasia, fulminant viral hepatitis, galactosemia, Gilbert's syndrome, glycogen storage diseases, graft-versus-host disease, granulomatous hepatitis, hemangioma, hemangiosarcoma, hemochromatosis, hepatic adenoma, hepatic amebiasis, hepatic encephalopathy, hepatic failure, hepatic schistosomiasis, hepatic veno-occlusive disease, hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E, hepatoblastoma, hepatocellular adenoma, hepatocellular carcinoma, hepatocellular necrosis, hepatorenal syndrome, hereditary fructose intolerance, hereditary hemochromatosis, herpesvirus hepatitis, hydatid cyst, hyperplastic lesions, hypoalbuminemia, infantile hemangioendothelioma, infarction of the liver, infectious mononucleosis hepatitis, inflammatory pseudotumor of the liver, intrahepatic cholangiocarcinoma, intrahepatic cholestasis, intrahepatic portal hypertension, ischemic necrosis (ischemic hepatitis), isoniazid-induced necrosis, jaundice, leptospirosis, liver cell adenoma, liver manifestations of Rocky Mountain spotted fever, macronodular cirrhosis, macrovesicular steatosis, malignant vascular neoplasms, mass lesions, massive hepatocellular necrosis, massive necrosis, mesenchymal hamartoma, metastatic tumors, micronodular cirrhosis, microvesicular steatosis, neonatal (physiologic) jaundice, neonatal hepatitis, neoplastic lesions, nodular transformation (nodular regenerative hyperplasia), nonsuppurative infections, nutritional cirrhosis, nutritional liver disease, oriental cholangiohepatitis, parasitic infestation of the liver, peliosis hepatis, porphyria cutanea tarda, portal hypertension, portal vein thrombosis, posthepatic portal hypertension, predictable (dose-related) toxicity, prehepatic portal hypertension, primary biliary cirrhosis, primary sclerosing cholangitis, pyogenic liver abscess, Q-fever hepatitis, Rotor's syndrome, sclerosing bile duct adenoma, sclerosing cholangitis, secondary hemochromatosis, submassive necrosis, syphilis, toxic liver injury, tyrosinemia, undifferentiated sarcoma, unpredictable (idiosyncratic) toxicity, vascular

lesions, virus-induced cirrhosis, Wilson's disease, and zonal necrosis.

405. The method of any of claims 79-84, 202-204, and 295-300, wherein said lung disease or disorder is selected from the group consisting of abnormal diffusion, abnormal perfusion, abnormal ventilation, accelerated silicosis, actinomycosis, acute air space pneumonia (acute bacterial pneumonia), acute bronchiolitis, acute congestion, acute infections of the lung, acute interstitial pneumonia, acute necrotizing viral pneumonia, acute organic dust toxic syndrome, acute pneumonia, acute radiation pneumonitis, acute rheumatic fever, acute silicosis, acute tracheobronchitis, adenocarcinoma, adenoid cystic carcinoma, adenosquamous carcinoma, adenovirus, adult respiratory distress syndrome (shock lung), agenesis, AIDS, air embolism, allergic bronchopulmonary mycosis, allergic granulomatosis and angiitis (Churg-Strauss), allograft rejection, aluminum pneumoconiosis, alveolar microlithiasis, alveolar proteinosis, amebic lung abscess, amniotic fluid embolism, amyloidosis of the lung, anomalies of pulmonary vasculature, anomalous pulmonary venous return, apiration pneumonia, aplasia, asbestosis, asbestos-related diseases, aspergillosis, asthma, atelectasis, atriovenous fistulas, atypical mycobacterial infection, bacteremia, bacterial pneumonia, benign clear cell tumor, benign epithelial tumors, benign fibrous mesothelioma, berylliosis, blastomycosis, bronchial atresia, bronchial asthma, bronchial carcinoid tumor, bronchial isomerism, bronchial obstruction, bronchial stenosis, bronchiectasis, bronchiolalveolar carcinoma, bronchiolitis, bronchiolitis obliterans-organizing pneumonia, bronchocentric granulomatosis, bronchogenic cyst, bronchopneumonia, bronchopulmonary dysplasia, bronchopulmonary sequestration, bullae, bullous emphysema, cancer, carcinoid tumors, carcinoma of the lung (bronchogenic carcinoma), central (bronchogenic) carcinoma, central cyanosis, centriacinar emphysema, cetrilobular emphysema, chest pain, Chlamydial pneumonia, chondroid hamartoma, chronic airflow obstruction, chronic bronchitis, chronic diffuse interstitial lung disease, chronic idiopathic pulmonary fibrosis, chronic lung abscess, chronic obstructive pulmonary diseases, chronic radiation pneumonitis, chronic silicosis, chylothorax, ciliary dyskinesia, coal worker's pneumoconiosis (anthracosis), coccidioidomycosis, collagen-vascular diseases, common cold, compensatory

emphysema, congenital acinar dysplasia, congenital alveolar capillary dysplasia, congenital bronchobiliary fistula, congenital bronchoesophageal fistula, congenital cystic adenomatoid malformation, congenital pulmonary lymphangiectasis, congenital pulmonary overinflation (congenital emphysema), congestion, cough, cryptococcosis, cyanosis, cystic fibrosis, cysticercosis, cytomegalovirus, desquamative interstitial pneumonitis, destructive lung disease, diatomaceous earth pneumoconiosis, diffuse alveolar damage, diffuse pulmonary hemorrhage, diffuse septal amyloidosis, diffuse panbronchiolitis, *Dirofilaria immitis*, diseases of the pleura, distal acinar (paraceptal) emphysema, drug-induced asthma, drug-induced diffuse alveolar damage, dyspnea, ectopic hormone syndromes, emphysema, empyema, eosinophilic pneumonias, exercise-induced asthma, extralobar sequestration, extrinsic allergic asthma, fat emboli, focal dust emphysema, follicular bronchiolitis, follicular bronchitis, foreign-body embolism, Fuller's earth pneumoconiosis, functional resistance to arterial flow (vasoconstriction), fungal granulomas of the lung, fungal infections, Goodpasture's syndrome, graphite pneumoconiosis, gray hepatization, hamartomas, hard metal disease, hemoptysis, hemothorax, herniation of lung tissue, herpes simplex, heterotopic tissues, high-altitude pulmonary edema, histoplasmosis, horseshoe lung, humidifier fever, hyaline membrane disease, hydatid cysts, hydrothorax, hypersensitivity pneumonitis (extrinsic allergic alveolitis), hypoxic vascular remodeling, iatrogenic drug-, chemical-, or radiation-induced interstitial fibrosis, idiopathic interstitial pneumonia, idiopathic organizing pneumonia, idiopathic pulmonary fibrosis (fibrosing alveolitis, Hamman-Rich syndrome, acute interstitial pneumonia), idiopathic pulmonary hemosiderosis, immunologic interstitial fibrosis, immunologic interstitial pneumonitis, immunologic lung disease, infections causing chronic granulomatous inflammation, infections causing chronic suppurative inflammation, infections of the air passages, infiltrative lung disease, inflammatory lesions, inflammatory pseudotumors, influenza, interstitial diseases of uncertain etiology, interstitial lung disease, interstitial pneumonitis in connective tissue diseases, intralobar sequestration of the lung (congenital), intrinsic (nonallergic) asthma, invasive pulmonary aspergillosis, kaolin pneumoconiosis, Kartagener's syndrome, *Klebsiella pneumoniae*, Langerhans' cell histiocytosis (histiocytosis X), large cell undifferentiated carcinoma, larval migration of *Ascaris*

lumbricoides, larval migration of *Strongyloides stercoralis*, left pulmonary artery “sling”, *Legionella pneumonia*, lipid pneumonia, lobar pneumonia, localized emphysema, long-standing bronchial obstruction, lung abscess, lung collapse, lung fluke, lung transplantation implantation response, lymphangiomyomatosis, lymphocytic interstitial pneumonitis (pseudolymphoma, lymphoma, lymphomatoid granulomatosis, malignant mesothelioma, massive pulmonary hemorrhage in the newborn, measles, meconium aspiration syndrome, mesenchymal cystic hamartomas, mesenchymal tumors, mesothelioma, metal-induced lung diseases, metastatic calcification, metastatic neoplasms, metastatic ossification, mica pneumoconiosis, mixed dust fibrosis, mixed epithelial-mesenchymal tumors, mixed type neoplasms, mucoepidermoid tumor, mucoviscidosis (fibrocystic disease of the pancreas, *Mycoplasma pneumoniae*, necrotizing bacterial pneumonia, necrotizing sarcoid granulomatosis, neonatal respiratory distress syndrome, neoplasms of the pleura, neuromuscular syndromes, nocardiosis, nondestructive lung disease, North American blastomycosis, occupational asthma, organic dust disease, panacinar emphysema, Pancoast’s syndrome, paracoccidioidomycosis, parainfluenza, paraneoplastic syndromes, paraseptal emphysema (paracicatricial), parasilicosis syndromes, parasitic infections of the lung, peripheral cyanosis, peripheral lung carcinoma, persistent pulmonary hypertension of the newborn, pleural diseases, pleural effusion, pleural plaques, pneumococcal pneumonia, pneumoconioses (inorganic dust diseases), *Pneumocystis carinii* pneumonia, pneumocystosis, pneumonitis, pneumothorax, precapillary pulmonary hypertension, primary (childhood) tuberculosis, primary (idiopathic) pulmonary hypertension, primary mesothelial neoplasms, primary pulmonary hypertensions, progressive massive fibrosis, psittacosis, pulmonary actinomycosis, pulmonary air-leak syndromes, pulmonary alveolar proteinosis, pulmonary arteriovenous malformation, pulmonary blastoma, pulmonary capillary hemangiomatosis, pulmonary carcinosarcoma, pulmonary edema, pulmonary embolism, pulmonary eosinophilia, pulmonary fibrosis, pulmonary hypertension, pulmonary hypoplasia, pulmonary infarction, pulmonary infiltration and eosinophilia, pulmonary interstitial air (pulmonary interstitial emphysema), pulmonary lesions, pulmonary nocardiosis, pulmonary parenchymal anomalies, pulmonary thromboembolism, pulmonary tuberculosis, pulmonary vascular disorders, pulmonary

vasculitides, pulmonary veno-occlusive disease, pyothorax, radiation pneumonitis, recurrent pulmonary emboli, red hepatization, respiration failure, respiratory syncytial virus, Reye's syndrome, rheumatoid lung disease, Rickettsial pneumonia, rupture of pulmonary arteries, sarcoidosis, scar cancer, scimitar syndrome, scleroderma, sclerosing hemangioma, secondary (adult) tuberculosis, secondary bacterial pneumonia, secondary pleural neoplasms, secondary pulmonary hypertension, senile emphysema, siderosis, silicate pneumoconiosis asbestosis, silicatoses, silicosis, simple nodular silicosis, Sjögren's syndrome, small airway lesions, small cell carcinoma, small cell undifferentiated (oat cell) carcinoma, spontaneous pneumothorax, sporotrichosis, sputum production, squamous (epidermoid) carcinoma, stannosis, staphylococcal pneumonia, suppuration (abscess formation), systemic lupus erythematosus, talcosis, tension pneumothorax, tracheal agenesis, tracheal stenosis, tracheobronchial amyloidosis, tracheobronchomegaly, tracheoesophageal fistula, transient tachypnea of the newborn (neonatal wet lung), tungsten carbide pneumoconiosis, usual interstitial pneumonia, usual interstitial pneumonitis, varicella, viral pneumonia, visceral pleural thickening, Wegener's granulomatosis, and whooping cough (pertussis).

406. The method of any of claims 85-90, 205-207, 301-306, wherein said muscular disease or disorder is selected from the group consisting of abnormalities of ion channel closure, acetylcholine receptor deficiency, acetylcholinesterase deficiency, acid maltase deficiencies (type 2 glycogenosis), acquired myopathies, acquired myotonia, adult myotonic dystrophy, alveolar rhabdomyosarcoma, aminoglycoside drugs, amyloidosis, amyotrophic lateral sclerosis, antimyelin antibodies, bacteremic myositis, Batten's disease (neuronal ceroid lipofuscinoses), Becker's muscular dystrophy, benign neoplasms, Bornholm disease, botulism, branching enzyme deficiency (type 4 glycogenosis), carbohydrate storage diseases, carnitine deficiencies, carnitine palmitoyltransferase deficiency, central core disease, centronuclear (myotubular) myopathy, Chagas' disease, chondrodystrophic myotonia, chronic renal disease, congenital fiber type disproportion, congenital muscular dystrophy, congenital myopathies, congenital myotonic dystrophy, congenital paucity of synaptic clefts, cysticercosis, cytoplasmic body myopathy, debranching enzyme deficiency (type 3

glycogenosis), defect in acetylcholine synthesis, denervation, dermatomyositis, diabetes mellitus, diphtheria, disorders of glycolysis, disorders of neuromuscular junction, distal muscular dystrophy, drug induced inflammatory myopathy, Duchenne muscular dystrophy, embryonal rhabdomyosarcoma, Emery-Dreifuss muscular dystrophy, exotoxic bacterial infections, facioscapulohumeral muscular dystrophy, failure of neuromuscular transmission, fiber necrosis, fibromyalgia, fingerprint body myopathy, Forbe's disease, gas gangrene, Guillain-Barré syndrome, inclusion body myositis, infantile spinal muscular atrophies, infectious myositis, inflammatory myopathies, influenza, Isaac's syndrome, ischemia, Kearns-Sayre syndrome, lactase dehydrogenase deficiency, Lambert-Eaton syndrome, Leigh's disease, leuknock outdystrophies, limb girdle muscular dystrophy, lipid storage myopathies, Luft's disease, lysosomal glycogen storage disease with normal acid maltase activity, malignant neoplasms, malignant hyperthermia, McArdle's disease, MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokes), MERRF syndrome (myoclonus epilepsy with ragged-red fibers), metabolic myopathies, microfibrillar myopathy, mitochondrial myopathies, multicore disease (minicore disease), multisystem triglyceride storage disease, muscle wasting from diabetes, muscular dystrophies, myasthenia gravis, myasthenic syndrome (Eaton-Lambert syndrome), myoadenylate deaminase deficiency, myoglobinuria, myopathies, myophosphorylase deficiency (type 5 glycogenosis), myositis, myositis ossificans, myotonia congenita, myotonic muscular dystrophy, nemaline myopathy, ocular muscular dystrophy, oculopharyngeal muscular dystrophy, paramyotonia, parasitic myopathies, periodic paralysis, peripheral neuropathies, phosphofructokinase deficiency (type 7 glycogenosis), phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, pleomorphic rhabdomyosarcoma, polymyositis, Pompe's disease, progressive muscular atrophy, progressive systemic sclerosis, reducing body myopathy, Refsum's disease, rhabdomyolysis, rhabdomyoma, rhabdomyosarcoma, sarcoidosis, sarcoma botryoides, sarcotubular myopathy, secondary congenital myopathies, slow channel syndrome, spasmodic torticollis, spheroid body myopathy, spinal muscular atrophy, steroid myopathy, stiff-person syndrome, systemic lupus erythematosus, Tauri's disease, tick paralysis, toxic myopathies, toxoplasmosis, trichinosis, trilaminar fiber myopathy, type 2 myofiber atrophy, typhoid fever, vasculitis,

viral myositis, and zebra body myopathy.

407. The method of any of claims 91-96, 208-210, and 307-312, wherein said disease or disorder of the ovary is selected from the group consisting of autoimmune oophoritis, brenner tumors, choriocarcinoma, clear cell adenocarcinoma, clear cell carcinoma, corpus luteal cysts, decidual reaction, dysgerminoma, embryonal carcinoma, endometrioid tumors, endometriosis, endometriotic cysts, epithelial inclusion cysts, fibrothecoma, follicular cysts, gonadoblastoma, granulosa-stroma cell tumors, granulosa-theca cell tumor, gynandroblastoma, hilum cell hyperplasia, luteal cysts, luteal hematomas, luteoma of pregnancy, massive ovarian edema, metastatic neoplasm, mixed germ cell tumors, monodermal tumors, mucinous tumors, neoplastic cysts, ovarian changes secondary to cytotoxic drugs and radiation, ovarian fibroma, polycystic ovary syndrome, pregnancy luteoma, premature follicle depletion, pseudomyxoma peritonei, resistant ovary, serous tumors, Sertoli-Leydig cell tumor, sex-cord tumor with annular tubules, steroid (lipid) cell tumor, stromal hyperplasia, stromal hyperthecosis, teratoma, theca lutein cysts, thecomas, transitional cell carcinoma, undifferentiated carcinoma, and yolk sac carcinoma (endodermal sinus tumor).

408. The method of any of claims 97-102, 211-213, and 313-318, wherein said blood disease or disorder is selected from the group consisting of abnormal hemoglobins, abnormalities in granulocyte count, abnormalities in lymphocyte count, abnormalities in monocyte count, abnormalities of blood platelets, abnormalities of platelet function, acanthocytosis, acquired neutropenia, acute granulocytic leukemia, acute idiopathic thrombocytopenic purpura, acute infections, acute lymphoblastic leukemia, acute lymphocytic leukemia, acute myeloblastic leukemia, acute myelocytic leukemia, acute myeloid leukemia, acute pyogenic bacterial infections, acute red cell aplasia, acute response to endotoxin, adult T-cell leukemia/lymphoma, afibrinogenemia, alpha thalassemia, altered affinity of hemoglobin for oxygen, amyloidosis, anemia, anemia due to acute blood loss, anemia due to chronic blood loss, anemia of chronic disease, anemia of chronic renal failure, anemias associated with enzyme deficiencies, anemias associated with erythrocyte cytoskeletal defects, anemias caused by inherited

disorders of hemoglobin synthesis, angiogenic myeloid metaplasia, aplastic anemia, ataxia-telangiectasia, Auer rods, autoimmune hemolytic anemias, B-cell chronic lymphocytic leukemia, B-cell chronic lymphoproliferative disorders, Bernard-Soulier disease, beta thalassemia, Blackfan-Diamond disease, brucellosis, Burkitt's lymphoma, Chédiak-Higashi syndrome, cholera, chronic acquired pure red cell aplasia, chronic granulocytic leukemia, chronic granulomatous disease, chronic idiopathic myelofibrosis, chronic idiopathic thrombocytopenic purpura, chronic lymphocytic leukemia, chronic lymphoproliferative disorders, chronic myelocytic leukemia, chronic myelogenous leukemia, chronic myeloid leukemia, chronic myeloproliferative disorders, congenital dyserythropoietic anemias, congenital dysfibrinogenemia, congenital neutropenia, corticosteroids, cyclic neutropenia, cytoplasmic maturation defect, deficiency of coagulation factors, delta-beta thalassemia, diphtheria, disorders of blood coagulation, disseminated intravascular coagulation & fibrinolysis, Döhle bodies, drug & chemical-induced hemolysis, drug-induced thrombocytopenia, drugs that suppress granulopoiesis, E. coli, early preleukemic myeloid leukemia, eosinophilia, eosinophilic granuloma, erythrocyte enzyme deficiency, erythrocyte membrane defects, essential thrombocythemia, factor 7 deficiency, familial cyclic neutropenia, Felty's syndrome, fibrinolytic activity, folate antagonists, folic acid deficiency, Gaucher disease, Glanzmann's thrombasthenia, glucose-6-phosphate dehydrogenase deficiency, granulated T-cell lymphocyte leukemia, granulocytic sarcoma, granulocytosis, Hageman trait, hairy cell leukemia (leukemic reticuloendotheliosis), Hand-Schüller-Christian disease, heavy-chain disease, hemoglobin C disease, hemoglobin constant spring, hemoglobin S, hemoglobinopathies, hemolysis caused by infectious agents, hemolytic anemia, hemolytic anemia secondary to mechanical erythrocyte destruction, hemolytic blood transfusion reactions, hemolytic disease of the newborn, hemophagocytic disorders, hemophilia A, hemophilia B (Christmas disease, factor 9 deficiency, hepatitis, hereditary elliptocytosis, hereditary spherocytosis, heterozygous beta thalassemia (Cooley's trait), homozygous beta thalassemia (Cooley's anemia), hypereosinophilic syndrome, hypoxia, idiopathic cold hemagglutinin disease, idiopathic thrombocytopenic purpura, idiopathic warm autoimmune hemolytic anemia, immune drug induced hemolysis, immune-mediated hemolytic anemias, immunodeficiency disease, infantile

neutropenia (Knock outstmann), instability of the hemoglobin molecule, iron deficiency anemia, isoimmune hemolytic anemia, juvenile chronic myeloid leukemia, Langerhans cell histiocytosis, large granular lymphocyte leukemia, lazy leukknock outcyte syndrome, Letterer-Siwe disease, leukemias, leukemoid reaction, leukknock outerythroblastic anemia, lipid storage diseases, lymphoblastosis, lymphocytopenia, lymphocytosis, lymphoma, lymphopenia, macroangiopathic hemolytic anemia, malaria, marrow aplasia, May-Hegglin anomaly, measles, megaloblastic anemia, metabolic diseases, microangiopathic hemolytic anemia, microcytic anemia, miliary tuberculosis, mixed phenotupe acute leukemia, monoclonal gammopathy of undetermined significance, monocytic leukemia, monocytosis, mucopolysaccharidosis, multiple myeloma, myeloblastic luekemia, myelodysplastic syndromes, myelofibrosis (agnogenic myeloid metaplasia), myeloproliferative diseases, myelosclerosis, neonatal thrombocytopenic purpura, neoplasms of hematopoietic cells, neutropenia, neutrophil dysfunction syndromes, neutrophil leukknock outcytosis, neutrophilia, Niemann-Pick disease, nonimmune drug-induced hemolysis, normocytic anemia, nuclear maturation defects, parahemophilia, paroxysmal cold hemogloiminuria, paroxysmal nocturnal hemoglobinuria, Pelger-Hüet anomaly, pernicious (Addisonian) anemia, plasma cell leukemia, plasma cell neoplasia, polycythemia, polycythemia rubra vera, presence of circulating anticoagulants, primary (idiopathic) thrombocythemia, primary neoplasms, prolymphocytic leukemia, Proteus, Pseudomonas, pure red cell aplasia, pyogenic bacterial infection, pyruvate kinase deficiency, radiation, red cell aplasia, refractory anemias, ricketsial infections, Rosenthal's syndrome, secondary absolute polycythemia, septicemia, severe combined immunodeficiency disease, Sézary syndrome, sickle cell disease, sickle cell-beta thalasse²mia, sideroblastic anemia, solitary plasmacytoma, storage pool disease, stress, structural hemoglobin variants, systemic lupus erythematosus, systemic mastocytosis, tart cell, T-cell chronic lymphoproliferative disorders, T-cell prolymphocytic leukemia, thalassemias, thrombocytopenia, thrombotic thrombocytopenic purpura, toxic granulation, toxic granules in severe infection, typhus, vitamin B12 deficiency, vitamin K deficiency, Von Willebrand's disease, Waldenstrom macroglobulinemia, and Wisknock outtt-aldrich syndrome.

409. The method of any of claims 103-108, 214-216, and 319-324, wherein said disease or disorder of the prostate is selected from the group consisting of acute bacterial prostatitis, acute prostatitis, adenoid basal cell tumor (adenoid cystic-like tumor), allergic (eosinophilic) granulomatous prostatitis, atrophy, atypical adenomatous hyperplasia, atypical basal cell hyperplasia, basal cell adenoma, basal cell hyperplasia, BCG-induced granulomatous prostatitis, benign prostatic hyperplasia, benign prostatic hypertrophy, blue nevus, carcinosarcoma, chronic abacterial prostatitis, chronic bacterial prostatitis, cribriform hyperplasia, ductal (endometrioid) adenocarcinoma, granulomatous prostatitis, hematuria, iatrogenic granulomatous prostatitis, idiopathic (nonspecific) granulous prostatitis, impotence, infectious granulomatous prostatitis, inflammatory pseudotumor, leiomyosarcoma, leukemia, lymphoepithelioma-like carcinoma, malaknock outplakia, malignant lymphoma, mucinous (colloid) carcinoma, nodular hyperplasia (benign prostatic hyperplasia), nonbacterial prostatitis, obstruction of urinary outflow, phyllodes tumor, postatrophic hyperplasia, postirradiation granulomatous prostatitis, postoperative spindle cell nodules, postsurgical granulomatous prostatitis, prostatic adenocarcinoma, prostatic carcinoma, prostatic intraepithelial neoplasia, prostatic melanosis, prostatic neoplasm, prostatitis, rhabdomyosarcoma, sarcomatoid carcinoma of the prostate, sclerosing adenosis, signet ring cell carcinoma, small-cell, undifferentiated carcinoma (high-grade neuroendocrine carcinoma), squamous cell carcinoma of the prostate, stromal hyperplasia with atypia, transitional cell carcinoma of the prostate, xanthogranulomatous prostatitis, and xanthoma.

410. The method of any of claims 109-114, 217-219, and 325-330, wherein said disease or disorder of the skin is selected from the group consisting of acanthosis nigricans, acne vulgaris, acquired epidermolysis bullosa, acrochordons, acrodermatitis enteropathica, acropustulosis, actinic keratosis, acute cutaneous lupus erythematosus, age spots, allergic dermatitis, alopecia areata, angioedema, angiokeratoma, angioma, anthrax, apocrine tumors, arthropid-bite reactions, atopic dermatitis, atypical fibroxanthoma, Bart's syndrome, basal cell carcinoma (basal cell epithelioma), Bateman's purpura, benign familial pemphigus (Hailey-Hailey disease), benign

keratoses, Berloque dermatitis, blue nevus, borderline leprosy, Borrelia infection (lyme disease), Bowen's disease (carcinoma in situ), bullous pemphigoid, Café-au-lait spot, calcification, cellular blue nevus, cellulitis, Chagas' disease, chickenpox (varicella), chloasma, chondrodermatitis nodularis helices, chondroid syringoma, chronic actinic dermatitis, chronic cutaneous lupus erythematosus, chronic discoid lesions, cicatricial pemphigoid, collagen abnormalities, compound melanocytic nevus, congenital melanocytic nevus, connective tissue nevus, contact dermatitis, cutaneous leishmaniasis, cutis laxa, cysts of the skin, dandruff, Darier's disease (keratosis follicularis), deep fungal infections, delayed-hypersensitivity reaction, dermal Spitz's nevus, dermatitis, dermatitis herpetiformis, dermatofibroma (cutaneous fibrous histiocytoma), dermatofibrosarcoma protuberans, dermatomyositis, dermatophyte infections, dermatophytid reactions, dermoid cyst, dermatropic rickettsial infections, dermatropic viral infections, desmoplastic melanoma, discoid lupus erythematosus, dominant dystrophic epidermolysis bullosa, Dowling-Meara epidermolysis bullosa, dyshidrotic dermatitis, dysplastic nevi, eccrine tumors, ecthyma, eczema, elastic tissue abnormalities, elastosis perforans serpiginosa, eosinophilic fasciitis, eosinophilic folliculitis, ephelides (freckles), epidermal cysts, epidermolysis bullosa, epidermolysis bullosa simplex, epidermotropic T-cell lymphoma, epidermotropic viruses, erysipelas, erythema multiforme, erythema nodosum, erythema nodosum leprosum, fibrotic disorders, fibrous tumors, follicular mucinosis, Fordyce's condition, fungal infections, genodermatoses, graft-versus-host disease, granuloma annulare, granulomatous vasculitis, Grover's disease, hair follicle infections, hair follicle tumors, hair loss, halo nevus, herpes simplex, herpes zoster (shingles), hidradenitis suppurativa, histiocytic lesions, HIV infections, hives, human papilloma virus, hyperhidrosis, ichthyosis, idiopathic skin diseases, impetigo, incontinentia pigmenti, intraepidermal spongiotic vesicles and bullae, invasive malignant melanoma, invasive squamous cell carcinoma, junctional epidermolysis bullosa, junctional melanocytic nevus, juvenile xanthogranuloma, Kaposi's sarcoma, keloids, keratinocytic lesions, keratinocytic tumors, keratoacanthoma, keratoderma blennorrhagicum, keratosis pilaris, leiomyoma, lentigo, lentigo maligna (Hutchinson's freckle), lepromatous leprosy, leprosy (Hansen's disease), leukocytoclastic vasculitis, lichen planus, lichen sclerosus et atrophicus,

lichen simplex chronicus, lichen striatus, lichenoid disorders, lichenoid drug reactions, light eruptions, linear bullous IgA dermatitis, lipoma, Lucio's phenomenon, lupus erythematosus, lymphatic filariasis, lymphocytic vasculitis, lymphocytoma cutis, lymphoid lesions, lymphomatoid papulosis, malignant blue nevus, malignant lymphomas, malignant melanoma, malignant melanoma in situ (noninvasive malignant melanoma), mast cell neoplasms, mastocytosis, measles, melanocyte disorders, melanocytic lesions, melanocytic neoplasms, melanocytic nevus, melanocytic nevus with dysplasia, melanotic macule, reactive type, melasma, merkel cell (neuroendocrine) carcinoma, metastatic melanoma, miliara, mixed connective tissue disease, molluscum contagiosum, morphea, mucin deposition, mucocutaneous leishmaniasis, mycetoma, mycobacterial infection, Mycobacterium marinum, Mycobacterium ulcerans, mycosis fungoides (cutaneous T cell lymphoma), myxoid cyst, necrobiosis lipoidica, necrobiosis lipoidica diabetorum, necrolytic migratory erythema, necrotizing fasciitis, neoplasms of dermal mesenchymal cells, neoplasms of keratinocytes, neoplasms of skin appendages, neoplasms of the epidermis, neural tumors, neuroendocrine carcinoma of the skin, neurothekeoma, nevocellular nevus (melanocytic nevus), nummular dermatitis, obliterative vasculitis, onchocerciasis, Paget's disease, pale cell acanthoma of Degos, palisaded encapsulated neuroma, papillomavirus infections, paraneoplastic pemphigus, parasitic infections, pemphigoid gestationis, pemphigus, pemphigus foliaceus, pemphigus vulgaris, perivascular infiltrates, pilar cysts, pinta, pityriasis alba, pityriasis lichenoides chronica (of Juliusberg), pityriasis lichenoides et varioliformis acuta, pityriasis rosea, pityriasis rubra pilaris, plantar warts, porokeratosis, pressure necrosis, progressive systemic sclerosis, protozoal infections, pruritic urticarial papules and plaques of pregnancy, pruritis ani, pseudofolliculitis barbae, pseudoxanthoma elasticum, psoriasis vulgaris, pyogenic granuloma, radial growth phase melanoma, recessive dystrophic epidermolysis bullosa, Reiter's syndrome, ringworm, Rochalimaea henselae infection, rosacea, rubella, sarcoidosis, scabies, Schamberg's disease, scleroderma, sebaceous hyperplasia, sebaceous tumors, seborrheic dermatitis, seborrheic keratosis, Sézary syndrome, skin manifestations of systemic diseases, small plaque parapsoriasis, smallpox (variola), solitary mastocytoma, spirochetal infections, Spitz's nevus, Spitz's nevus junctional type, squamous cell carcinoma, stasis dermatitis,

Stevens-Johnson syndrome, subacute cutaneous lupus erythematosus, subcorneal pustular dermatosis, superficial fungal infections, superficial spreading melanoma in situ, syphilis, syringoma, systemic lupus erythematosus, systemic mastocytosis, tinea (dermatophytosis, tinea versicolor, toxic epidermal necrolysis, transient acantholytic dermatosis, tuberculoid leprosy, tuberculosis, urticaria, urticaria pigmentosa, urticarial vasculitis, vascular tumors, verruca vulgaris (common wart), vertical growth type phase melanoma, visceral leishmaniasis, vitiligo, warty dyskeratoma, Weber-Cockayne epidermolysis bullosa, Woringer-Knock outflow disease, xanthomas, xeroderma pigmentosum, xerosis, and yaws.

411. The method of any of claims 115-120, 220-222, and 331-336, wherein said disease or disorder of the spleen is selected from the group consisting of abnormal immunoblastic proliferations of unknown origin, acute infections, acute parasitemias, agnogenic myeloid metaplasia, amyloidosis, angioimmunoblastic lymphadenopathy, antibody-coated cells, asplenia, autoimmune diseases, autoimmune hemolytic anemias, B-cell chronic lymphocytic leukemia and prolymphocytic leukemia, babesiosis, bone marrow involvement by carcinoma, brucellosis, carcinoma, ceroid histiocytosis, chronic alcoholism, chronic granulomatous disease, chronic hemolytic anemias, chronic hemolytic disorders, chronic immunologic inflammatory disorders, chronic infections, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic parasitemias, chronic uremia, cirrhosis, cold agglutinin disease, congestive splenomegaly, cryoglobulinemia, disseminated tuberculosis, dysproteinemias, endocrine disorders, erythroblastic leukemia, erythropoiesis, essential thrombocythemia, extramedullary hematopoiesis, Felty syndrome, fibrocongestive splenomegaly, fungal infections, gamma heavy-chain disease, Gaucher's disease, graft rejection, granulomatous infiltration, hairy cell leukemia, hamartomas, Hand-Schüller-Christian disease, hemangiomas, hemangiosarcomas, hematologic disorders, hemoglobinopathies, hemolytic anemias, hereditary elliptocytosis, hereditary spherocytosis, histiocytic medullary reticulosis, histiocytosis X, Hodgkin's disease, hypersensitivity reactions, hypersplenism, hyposplenism, idiopathic thrombocytopenic purpura, IgA deficiency, immune granulomas, immune thrombocytopenia, immune thrombocytopenic purpura,

immunodeficiency disorders, infection associated hemophagocytic syndrome, infectious granulomas, infectious mononucleosis, infective endocarditis, infiltrative splenomegaly, inflammatory pseudotumors, leishmaniasis, Leterer-Siwe disease, leukemia, lipogranulomas, lymphocytic leukemias, lymphoma, malabsorption syndromes, malaria, malignant lymphoma, megakaryoblastic leukemia, metastatic tumor, monocytic leukemias, mucopolysaccharidoses, multicentric Castleman's disease, multiple myeloma, myelocytic leukemias, myelofibrosis, myeloproliferative syndromes, neoplasms, Niemann-Pick disease, non-Hodgkin's lymphoma, parasitic disorders, parasitized red blood cells, peliosis, polycythemia rubra vera, portal vein congestion, portal vein stenosis, portal vein thrombosis, portal venous hypertension, rheumatoid arthritis, right-sided cardiac failure, sarcoidosis, sarcoma, secondary amyloidosis, secondary myeloid metaplasia, serum sickness, sickle-cell disease, splenic cysts, splenic infarction, splenic vein hypertension, splenic vein stenosis, splenic vein thrombosis, splenomegaly, storage diseases, systemic lupus erythematosus, systemic vasculitides, T-cell chronic lymphocytic leukemia, thalasemia, thrombocytopenic purpura, thyrotoxicosis, trapping of immature hematologic cells, tuberculosis, tumorlike conditions, typhoid fever, vascular tumors, vasculitis, and viral infections.

412. The method of any of claims 121-126, 223-225, and 337-342, wherein said disease or disorder of the stomach is selected from the group consisting of acute erosive gastropathy, acute gastric ulcers, adenocarcinomas, adenomas, adenomatous polyps, advanced gastric cancer, ampullary carcinoma, atrophic gastritis, bacterial gastritis, carcinoid tumors, carcinoma of the stomach, chemical gastritis, chronic (nonerosive) gastritis, chronic idiopathic gastritis, chronic nonatrophic gastritis, Chronkhite-Canada syndrome, congenital cysts, congenital diaphragmatic hernias, congenital diverticula, congenital duplications, congenital pyloric stenosis, congestive gastropathy, cyclic vomiting syndrome, decreased mucosal resistance to acid, diffuse or infiltrating adenocarcinoma, early gastric cancer, emphysematous gastritis, endocrine cell hyperplasia, environmental gastritis, eosinophilic gastritis, eosinophilic gastroenteritis, epithelial polyps, erosive (acute) gastritis, fundic gland polyps, fungal gastritis, gangliocytic paragangliomas, gastral antral vascular ectasia, gastric adenocarcinoma,

gastric outlet obstruction (pyloric stenosis), gastric ulcers, gastritis, gastroesophageal reflux, gastroparesis, granulomatous gastritis, H. Pylori infection, hamartomatous polyps, heterotopias, heterotopic pancreatic tissue, heterotopic polyps, hyperplastic gastropathy, hyperplastic polyps, hypersecretion of acid, infectious gastritis, inflammatory lesions of the stomach, inflammatory polyps, intestinal metaplasia, invasive carcinoma, ischemia, leiomyoma, linitis plastica, lumenally acting toxic chemicals, lymphocytic gastritis, lymphomas, malignant gastric stromal neoplasms, malignant lymphoma, malignant transformation of a benign gastric ulcer, Menentrier's disease (hypertrophic gastritis, rugal hypertrophy), mesenchymal neoplasms, metastatic tumors, mucosal polyps, myoepithelial adenomas, myoepithelial hamartomas, neoplasms, neuroendocrine hyperplasias, neuroendocrine tumors, nonerosive gastritis and stomach cancer, nonneoplastic polyps, parasitic gastritis, peptic ulcer disease, phlegmonous gastritis, plasma cell gastritis, polypoid (fungating) adenocarcinoma, poorly differentiated neuroendocrine carcinomas, precancerous lesions, Puetz-Jeghers syndrome, pyloric atresia, rapid gastric emptying, reflux of bile, stress ulcers, stromal tumors, superficial gastritis, type A chronic gastritis (autoimmune gastritis and pernicious anemia), type B chronic gastritis (chronic antral gastritis, H. Pylori gastritis), ulcerating adenocarcinoma, vasculitis, viral gastritis, xanthomatous gastritis, and Zollinger-Ellison syndrome.

413. The method of any of claims 127-132, 226-228, and 343-348, wherein said disease or disorder of the testes is selected from the group consisting of aberrant ducts of Haller, abnormal productions of hormones, abnormalities of testicular descent, acute epididymoorhchitis, adenomatoid tumor, adenomatous hyperplasia of the rete testis, adenovirus, administration of estrogens, adrenal rests, alcoholic cirrhosis, amyloidosis, anorchism, appendix testes, bacterial infections, Brucella, cachexia, carcinoma in situ, carcinoma of the rete testis, chlamydia, choriocarcinoma, choristomas, chronic fibrosing epididymoorchitis, coxsackie virus B, cryptorchidism, cystic dysplasia of the rete testis, cytomegalovirus, dystopia, E. coli, Echinococcus granulosus, ectopic testes, embryonal carcinoma, epididymoorchitis, Fournier's scrotal gangrene, fungal infection, germ cell aplasia, germ cell neoplasms, gonadal dysgenesis, gonadal stromal neoplasms,

granulomatous orchitis, granulosa cell tumors, Haemophilus influenzae, HIV, hypergonadism, hypogonadotropic hypogonadism, hypopituitarism, hypospermatogenesis, hydrocele, idiopathic granulomatous orchitis, incomplete maturation arrest, infarction, infertility, inflammatory diseases, inflammatory lesions, interstitial (Leydig) cell tumors, Klinefelter's syndrome, iatrogenic lesions, Leydig cell tumors, malakoplakia, malignant lymphoma, malnutrition, maturation arrest of spermatogenesis, metastatic tumors, mixed germ cell tumors, monorchism, mumps orchitis, mycobacteria, Neisseria gonorrhoeae, neoplasms, obstruction to outflow of semen, orchitis, parasitic infection, polyorchidism, radiation, Salmonella, sarcoidosis, Schistosoma haematobium, seminoma, Sertoli cell tumors, sex cord stromal tumors, sperm granuloma, spermatocytic seminoma, syphilis, teratocarcinoma, teratoma, testicular atrophy, testicular neoplasms, testicular torsion, Treponema pallidum, tuberculous epididymo-orchitis, tumors of nonspecific stroma, undescended testes, uropathogens, varicocele, vascular disturbances, vasculitis, viral infection, Wuchereria bancrofti, and yolk sac carcinoma.

414. The method of any of claims 133-138, 229-231, and 349-354, wherein said disease or disorder of the thymus is selected from the group consisting of accidental involution, acute accidental involution, acute lymphoblastic leukemia of T cell type, agenesis, age-related involution, anaplastic carcinoma, ataxia telangiectasia, atrophy, bacterial infections, bacterial mediastinitis, basaloid carcinoma, bone marrow transplantation, Bruton's agammaglobulinemia, carcinosarcoma, chronic accidental involution, clear cell carcinoma, cortical thymoma, cytomegalovirus, DiGeorge syndrome, dysgenesis, dysplasia with pattern similar to severe atrophy, dysplasia with pseudoglandular appearance, dysplasia with stromal conticomedullary differentiation, ectopia, germ cell tumors, Grave's disease, histiocytosis X, HIV, Hodgkin's disease, hyperplasia, infectious mononucleosis, involution, lymphoblastic lymphoma of T-cell type, lymphoepithelioma-like carcinoma, lymphofollicular thymitis, maldescent, malignant lymphomas, malignant thymoma, measles giant cell pneumonia, medullary thymoma, mixed (composite) thymoma, mucoepidermoid carcinoma, myasthenia gravis, neonatal syphilis, neoplasms, Omenn's syndrome, predominantly cortical (organoid)

thymoma, primary mediastinal B-cell lymphoma of high-grade malignancy, sarcomatoid carcinoma, seminoma, severe combined immunodeficiency, short limb dwarfism, simple dysplasia, small cell carcinoma, small-cell B-cell lymphoma of MALT type, squamous cell carcinoma, systemic lupus erythematosus, teratoma, thymic carcinoid, thymic carcinoma, thymic cysts, thymic epithelial cysts, thymic epithelial tumorw, thymic neoplasms, thymitis with diffuse B-cell infiltrations, thymolipoma, thymoma, true thymic hyperplasia, varicella-zoster, viral infections, well differentiated thymic carcinoma, and Wiscott-Aldrich syndrome.

415. The method of any of claims 139-144, 232-234, and 355-360, wherein said disease or disorder of the thyroid is selected from the group consisting of aberrant thyroid glands, accessory thyroid glands, adenoma with bizarre nuclei, agenesis, amphicrine variant of medullary carcinoma, anaplastic (undifferentiated) carcinoma, aplasia, atrophic thyroiditis, atypical adenoma, autoimmune thyroiditis, carcinoma, C-cell hyperplasia, clear cell tumors, clear cell variant of medullary carcinoma, colloid adenoma, columnar variant of papillary carcinoma, congenital hypothyroidism (cretinism), diffuse nontoxic goiter, diffuse sclerosing variant of papillary carcinoma, dyschoronogenic goiter, embryonal adenoma, encapsulated variant of papillary carcinoma, endemic cretinism, endemic goiter, enzyme deficiency, fetal adenoma, follicular adenoma, follicular carcinoma, follicular variant of medullary carcinoma, follicular variant of papillary carcinoma, fungal infection, giant cell variant of medullary carcinoma, goiter induced by antithyroid agents, goitrous hypothyroidism, Graves' disease, Hashimoto's autoimmune thyroiditis, Hürthle cell (oncocytic) adenoma, hyalinized trabecular adenoma, hyperthyroidism, hypothyroid cretinism, hypothyroidism, iodine deficiency, juvenile thyroiditis, latrogenic hypothyroidism, lingual thyroid glands, malignant lymphoma, medullary carcinoma, melanocytic variant of medullary carcinoma, mesenchymal tumors, metastatic tumors, minimally invasive follicular carcinoma, mixed medullary and follicular carcinoma, mixed medullary and papillary carcinoma, mucinous carcinoma, mucoepidermoid carcinoma, multinodular goiter, myxedema, neoplasms, neurologic cretinism, nonspecific lymphocytic (simple chronic) thyroiditis, oncocytic variant of medullary carcinoma, palpation thyroiditis,

papillary carcinoma, papillary microcarcinoma, papillary variant of medullary carcinoma, partial agenesis, pituitary thyrotropic adenoma, poorly differentiated carcinoma, primary hypothyroidism, pseudopapillary variant of medullary carcinoma, Riedel's thyroiditis, sclerosing mucoepidermoid carcinoma with eosinophilia, silent thyroiditis, simple adenoma, small cell variant of medullary carcinoma, solitary thyroid nodule, sporadic goiter, squamous cell carcinoma, squamous variant of medullary carcinoma, subacute thyroiditis (DeQuervain, granulomatous, giant cell thyroiditis), tall cell variant of papillary carcinoma, tertiary syphilis, thyroglossal duct cyst, thyroid agenesis, thyroid nodules, thyroiditis, thyrotoxicosis, toxic adenoma, toxic multinodular goiter, toxic nodular goiter (Plummer's disease), tuberculosis, tubular variant of medullary carcinoma, and widely invasive follicular carcinoma.

416. The method of any of claims 145-150, 235-237, and 361-366, wherein said disease or disorder of the uterus is selected from the group consisting of acute cervicitis, acute endometritis, adenocanthoma, adenocarcinoma, adenocarcinoma in situ, adenoid cystic carcinoma, adenomatoid tumor, adenomyoma, adenomyosis (endometriosis interna), adenosquamous carcinoma, amebiasis, arias-Stella phenomenon, atrophy of the endometrium, atypical hyperplasia, benign polypoid lesions, benign stromal nodule, carcinoid tumors, carcinoma in situ, cervical intraepithelial neoplasia, chlamydia, chronic cervicitis, chronic nonspecific endometritis, ciliated (tubal) metaplasia, clear cell adenocarcinoma, clear cell carcinoma, clear cell metaplasia, complex hyperplasia with atypia, complex hyperplasia without atypia, condyloma aduminatum, congenital abnormalities, corpus cancer syndrome, cystic hyperplasia, dysfunctional uterine bleeding, dysmenorrhea, dysplasia of the cervix (cervical intraepithelial neoplasia, squamous intraepithelial lesion), endocervical adenocarcinoma, endocervical polyp, endolymphatic stromal myosis, endometrial adenocarcinoma, endometrial carcinoma, endometrial hyperplasia, endometrial polyps, endometrial stromal neoplasms, endometriosis, endometritis, endometroid (pure) adenocarcinoma of the endometrium, endometroid adenocarcinoma with squamous differentiation, eosinophilic metaplasia, epimenorrhea, exogenous progestational hormone effect, extrauterine endometriosis (endometriosis externa), gestational trophoplastic disease, gonorrhea, hemangioma,

herpes simplex virus type 2, high-grade squamous intraepithelial lesion, human papillomavirus, hyperplasia, inadequate luteal phase, infertility, inflammatory cervical lesions, inflammatory lesions of the endometrium, intravenous leiomyomatosis, invasive carcinoma of cervix, invasive squamous cell carcinoma, leiomyoma, leiomyosarcoma, lipoma, low-grade squamous intraepithelial lesion, malignant mixed mesodermal (Müllerian) tumor, menorrhagia, metaplasia, metastasizing leiomyoma, metastatic carcinoma, microglandular hyperplasia, microinvasive carcinoma, microinvasive squamous cell carcinoma, mucinous adenocarcinoma, mucinous metaplasia, neoplasms of the cervix, neoplasms of the endometrium, neoplasms of the myometrium, nonneoplastic cervical proliferations, papillary syncytial metaplasia, papilloma, pelvic inflammatory disease, peritoneal leiomyomatosis, persistent luteal phase, postmenopausal bleeding, serous papillary adenocarcinoma, simple hyperplasia with atypia, simple hyperplasia without atypia, spontaneous abortion, squamous carcinoma, squamous cell neoplasia, squamous intraepithelial lesions, squamous metaplasia, squamous metaplasia (acanthosis), stromal sarcoma, tuberculous endometritis, unopposed estrogen effect, uterine leiomyomata, verrucous carcinoma, vestigial and heterotopic structures, villoglandular papillary adenocarcinoma, and viral endometritis.

417. The method of any of claims 151-156, 238-240, and 367-372, wherein said disease or disorder of the pancreas is selected from the group consisting of ACTHoma, acute pancreatitis, adult onset diabetes, annular pancreas, carcinoid syndrome, carcinoid tumors, carcinoma of the pancreas, chronic pancreatitis, congenital cysts, Cushing's syndrome, cystadenocarcinoma, cystic fibrosis (mucoviscidosis, fibrocystic disease), diabetes mellitus, ectopic pancreatic tissue, gastrinoma, gastrin excess, glucagon excess, glucagonomas, GRFomas, hereditary pancreatitis, hyperinsulinism, impaired insulin release, infected pancreatic necrosis, insulin resistance, insulinomas, islet cell hyperplasia, islet cell neoplasms, juvenile onset diabetes, macroamylasemia, maldevelopment of the pancreas, maturity-onset diabetes of the young, metastatic neoplasms, mucinous cystadenoma, neoplastic cysts, nonfunctional pancreatic endocrine tumors, pancreas divisum, pancreatic abscess, pancreatic cancer, pancreatic cholera, pancreatic cysts, pancreatic endocrine tumor causing carcinoid syndrome, pancreatic

endocrine tumor causing hypercalcemia, pancreatic endocrine tumors, pancreatic exocrine insufficiency, pancreatic pleural effusion, pancreatic polypeptide excess, pancreatic pseudocyst, pancreatic trauma, pancreatogenous ascites, serous cystadenoma, Shwachman's syndrome, somatostatin excess, somatostatinoma syndrome, traumatic pancreatitis, type 1 (insulin-dependent) diabetes, type 2 (non-insulin-dependent) diabetes, vasoactive intestinal polypeptide excess, VIPomas, Zollinger-Ellison syndrome.

418. The method of any of claims 157-162, 241-243, and 373-378, wherein said disease or disorder of the bone and joints is selected from the group consisting of achondroplasia, acute bacterial arthritis, acute pyogenic osteomyelitis, Albright's syndrome, alkaptonuria (ochronosis), aneurysmal bone cyst, ankylosing spondylitis, arthritic, arthropathies associated with hemoglobinopathies, arthropathy of acromegaly, arthropathy of hemochromatosis, bone cysts, calcium hydroxyapatite deposition disease, calcium pyrophosphate deposition disease, chondrocalcinosis, chondroma, chondrosarcoma, chondrochondritis, chondromblastoma, congenital dislocation of the hip, congenital disorders of joints, echondromatosis (dyschondroplasia, Ollier's disease), erosive osteoarthritis, Ewing's sarcoma, Felty's syndrome, fibromyalgia, fibrous cortical defect, fibrous dysplasia (McCune-Albright syndrome, fungal arthritis, ganglion, giant cell tumor, gout, hematogenous osteomyelitis, hemophilic arthropathy, hereditary hyperphosphatasia, hyperostosis, hyperostosis frontalis interna, hyperparathyroidism (osteitis fibrosa cystica), hypertrophic osteoarthropathy, infections diseases of joints, juvenile rheumatoid arthritis (Still's disease), Lyme disease, lymphoid neoplasms, melorheostosis, metabolic diseases of joints, metastatic carcinoma, metastatic neoplasms, monostatic fibrous dysplasia, multiple exostoses (diaphyseal aclasis, osteochondromatosis), neoplasms, neuropathic joint (Charcot's joint), osteoarthritis, osteoarthrosis, osteoblastoma, osteochondroma (exostosis), osteogenesis imperfecta (brittle bone disease), osteoid osteoma, osteoma, osteomalacia, osteomyelitis, osteomyelosclerosis, osteopetrosis (marble bone disease, Albers-Schönberg disease), osteopoikilosis, osteoporosis (osteopenia), osteosarcoma, osteosclerosis, Paget's disease of bone (osteitis deformans), parasitic arthritis, parosteal osteosarcoma, pigmented

villonodular synovitis, polyostotic fibrous dysplasia, postinfectious or reactive arthritis, progressive diaphyseal dysplasia (Camurati-Engelmann disease), pseudogout, psoriatic arthritis, pyknodysostosis, pyogenic arthritis, reflex sympathetic dystrophy syndrome, relapsing polychondritis, rheumatoid arthritis, rickets, senile osteoporosis, sickle cell disease, spondyloepiphyseal dysplasia, synovial chondromatosis, synovial sarcoma, syphilitic arthritis, talipes calcaneovalgus, talipes equinovarus, thalassemia, Tietze's syndrome, tuberculosis of bone, tuberculous arthritis, unicameral bone cyst (solitary bone cyst), viral arthritis.

419. The method of any of claims 163-168, 244-246, and 379-384, wherein said disease or disorder of the breast is selected from the group consisting of acute mastitis, breast abscess, carcinoma, chronic mastitis, congenital breast anomalies, cystic mastopathy, ductal carcinoma, ductal carcinoma in situ, ductal papilloma, fat necrosis, fibroadenoma, fibrocystic changes, fibrocystic disease, galactorrhea, granular cell tumor, gynecomastia, infiltrating ductal carcinoma, inflammatory breast carcinoma, inflammatory breast lesions, invasive lobular carcinoma, juvenile hypertrophy of the breast, lactating adenoma, lobular carcinoma in situ, neoplasms, Paget's disease of the nipple, phyllodes tumor (cystosarcome phyllodes), polymastia, polymazia, polythelia, silicone granuloma, supernumerary breast, and supernumerary nipples.

420. The method of any of claims 169-174, 247-249, and 385-390, wherein said disease or disorder of the immune system is selected from the group consisting of abnormal neutrophil function, acquired immunodeficiency, acute rejection, Addison's disease, advanced cancer, aging, allergic rhinitis, angioedema, arthrus-type hypersensitivity reaction, ataxia-telangiectasia, autoimmune disorders, autoimmune gastritis, autosomal recessive agammaglobulinemia, blood transfusion reactions, Bloom's syndrome, Bruton's congenital agammaglobulinemia, bullous pemphigoid, Chédiak-Higashi syndrome, chronic active hepatitis, chronic granulomatous disease of childhood, chronic rejection, chronic renal failure, common variable immunodeficiency, complement deficiency, congenital (primary) immunodeficiency, contact dermatitis, deficiencies of immune response, deficiency of the vascular response, dermatomyositis,

diabetes mellitus, disorders of microbial killing, disorders of phagocytosis, Goodpasture's syndrome, graft rejection, graft-versus-host disease, granulocyte deficiency, granulocytic leukemia, Graves' disease, Hashimoto's thyroiditis, hemolytic anemia, hemolytic disease of the newborn, HIV infection (AIDS), Hodgkin's disease, hyperacute rejection, hyper-IgE syndrome, hypersensitivity pneumonitis, hypoparathyroidism, IgA deficiency, IgG subclass deficiencies, immunodeficiency with thymoma, immunoglobulin deficiency syndromes, immunologic hypersensitivity, immunosuppressive drug therapy, infertility, insulin-resistant diabetes mellitus, interferon γ receptor deficiency, interleukin 12 receptor deficiency, iron deficiency, juvenile insulin-dependent diabetes mellitus, Kaposi's sarcoma, lazy leukocyte syndrome, localized type 1 hypersensitivity, lymphocytic leukemia, lymphoma, malignant B cell lymphoma, major histocompatibility complex class 2 deficiency, mixed connective tissue disease, multiple myeloma, myasthenia gravis, myeloperoxidase deficiency, neutropenia, nude syndrome, pemphigus vulgaris, pernicious anemia, postinfectious immunodeficiency, primary biliary cirrhosis, primary immunodeficiency, primary T cell immunodeficiency, progressive systemic sclerosis, protein-calorie malnutrition, purine nucleoside phosphorylation deficiency, rheumatic fever, rheumatoid arthritis, secondary immunodeficiency, selective (isolated) IgA deficiency, serum sickness type hypersensitivity reaction, severe combined immunodeficiency, Sjögren's syndrome, sympathetic ophthalmitis, systemic lupus erythematosus, systemic mastocytosis, systemic type 1 hypersensitivity, T cell receptor deficiency, T lymphopenia (Nezelof's syndrome), thrombocytopenia, thymic hypoplasia (DiGeorge syndrome), thymic neoplasms, thymoma (Goode's syndrome), transient hypogammaglobulinemia of infancy, type 1 (immediate) hypersensitivity (atopy, anaphylaxis), type 2 hypersensitivity, type 3 hypersensitivity (immune complex injury), type 4 (delayed) hypersensitivity, urticaria, variable immunodeficiency, vitiligo, Wiskott-Aldrich syndrome, x-linked agammaglobulinemia, x-linked immunodeficiency with hyper IgM, x-linked lymphoproliferative syndrome, zap70 tyrosine kinase deficiency.

421. The method of any of claims 175-180, 250-252, and 391-396, wherein said metabolic or nutritive disease or disorder is selected from the group consisting of 5,10-

methylenetetrahydrofolate reductase deficiency, achondrogenesis type 1B, acid α -1,4 glucosidase deficiency, acquired generalized lipodystrophy (Lawrence syndrome), acquired partial lipodystrophy (Barraquer-Simons syndrome), acute intermittent porphyria, acute panniculitis, adenine phosphoribosyltransferase deficiency, adenosine deaminase deficiency, adenylosuccinate lyase deficiency, adiposis dolorosa (Dercum disease), ALA dehydratase-deficient porphyria, albinism, alkaptonuria, amulopectinosis, Andersen disease, argininemia, argininosuccinic aciduria, astelosteogenesis type 2, Bartter's syndrome, benign familial neonatal epilepsy, benign fructosuria, benign recurrent and progressive familial intrahepatic cholestasis, biotin deficiency, branching enzyme deficiency, calcium deficiency, carnitine transport defect, choline deficiency, choline toxicity, chromium deficiency, chronic fat malabsorption, citrullinemia, classic branched-chain ketoaciduria, classic cystinuria, congenital chloridorrhea, congenital erythropoietic porphyria, congenital generalized lipodystrophy, congenital myotonia, copper deficiency, copper toxicity, cystathionine β -synthase deficiency, cystathioninuria, cystic fibrosis, cystinosis, cystinuria, Darier disease, defect in transport of long-chain fatty acids, deficiency of cobalamin coenzyme deficiency, Dent's syndrome, diatrophic dysplasia, dibasic aminoaciduria, dicarboxylic aminoaciduria, dihydropyrimidine dehydrogenase deficiency, distal renal tubular acidosis, dry beriberi, Dubin-Johnson syndrome, dysbetalipoproteinemia, end-organ insensitivity to vitamin D, erythropoietic protoporphyria, Fabry disease, failure of intestinal absorption, familial apoprotein C2 deficiency, familial combined hyperlipidemia, familial defective Apo B100, familial goiter, familial hypercholesterolemia, familial hypertriglyceridemia, familial hypophosphatemic rickets, familial lipoprotein lipase deficiency, familial partial lipodystrophy, Fanconi-Bickel syndrome, fluoride deficiency, folate malabsorption, folic acid deficiency, formiminoglutamic aciduria, fructose 1,6 diphosphatase deficiency, galactokinase deficiency, galactose 1-phosphate uridyl transferase deficiency, galactosemia, Gaucher disease, Gitelman's syndrome, globoid cell leukodystrophy, glucose-6-phosphatase deficiency, glucose-6-translocase deficiency, glucose-galactose malabsorption, glucose-transporter protein syndrome, glutaric aciduria, glycogen storage disease type 2, glycogen storage disease type 1b, glycogen storage disease type 1d, glycogen synthase deficiency, gout, Hartnup disease, hawkinsinuria,

hemochromatosis, hepatic glycogenosis with renal fanconi syndrome, hepatic lipase deficiency, hepatic porphyria, hereditary coproporphyria, hereditary fructose intolerance, hereditary xanthinuria, Hers disease, histidinemia, histidinuria, HIV-1 protease inhibitor-induced lipodystrophy, homocitrullinuria, homocystinuria, homocystinuria, homocystinuria and methylmalonic acidemia, homocystinurias, Hunter syndrome, Hurler disease, Hurler-Scheie disease, hypophosphatemic rickets, hyperammonemia, hyperammonemia, hypercholesterolemia, hypercystinuria, hyperglycinemia, hyperhydroxyprolinemia, hyperkalemic periodic paralysis, hyperleucineisoleucinemia, hyperlipoproteinemias, hyperlysinemia, hypermagnesemia, hypermetabolism, hypermethioninemia, hyperomithinemia, hyperoxaluria, hyperphenylalaninemia with primapterinuria, hyperphenylalaninemias, hyperphosphatemia, hyperprolinemia, hypertriglyceridemia, hyperuricemia, hypervalinemia, hypervitaminosis A, hypervitaminosis D, hypocholesterolemia, hypometabolism, hypophosphatemia, hypouricemia, hypovitaminosis A, hypoxanthine phosphoribosyltransferase deficiency, iminoglycinuria, iminopeptiduria, intermittent branched-chain ketoaciduria, intestinal malabsorption, iodine deficiency, iron deficiency, isovaleric acidemia, Jervell and Lange-Nielsen syndrome, juvenile pernicious anemia, keshan disease, Knock out, knock out's syndrome, kwashiorkor, leukodystrophies, Liddle's syndrome, lipodystrophies, lipomatosis, liver glycogenoses, liver phosphorylase kinase deficiency, long QT syndrome, lysinuria, lysosomal storage diseases, magnesium deficiency, malabsorptive diseases, malignant hyperphenylalaninemia, manganese deficiency, marasmus, Maroteaux-Lamy disease, McArdle disease, Menkes' disease, metachromatic leukodystrophy, methionine malabsorption, methylmalonic acidemia, molybdenum deficiency, monosodiumurate gout, Morquio syndrome, mucopolysaccharidoses, mucopolysaccharidoses, multiple carboxylase deficiency syndrome, multiple symmetric lipomatosis (Madelung disease), muscle glycogenoses, muscle phosphofructokinase deficiency, muscle phosphorylase deficiency, myoadenylate deaminase deficiency, nephrogenic diabetes insipidus, nesidioblastosis of pancreas, niacin deficiency, niacin toxicity, Niemann-Pick disease, obesity, orotic aciduria, osteomalacia, paramyotonia congenita, pellagra, Pendred syndrome, phenylketonuria, phenylketonuria type 1, phenylketonuria type 2, phenylketonuria type 3, phosphate

deficiency, phosphoribosylpyrophosphate synthetase overactivity, polygenic hypercholesterolemia, Pompe disease, porphyria cutanea tarda, porphyrias, primary bile acid malabsorption, primary hyperoxaluria, primary hypoalphalipoproteinemia, propionic acidemia, protein-energy malnutrition, proximal renal tubular acidosis, purine nucleoside phosphorylase deficiency, pyridoxine deficiency, pyrimidine 5'-nucleotidase deficiency, renal glycosuria, riboflavin deficiency, rickets, Rogers' syndrome, saccharopinuria, Sandhoff disease, Sanfilippo syndromes, sarcosinemia, Scheie disease, scurvy (vitamin C deficiency), selenium deficiency, selenosis, sialic acid storage disease, S-sulfo-L-cysteine, sulfite, thiosulfaturia, Tarui disease, Tay-Sachs disease, thiamine deficiency, tryptophan malabsorption, tryptophanuria, type 1 pseudohypoaldosteronism, type 3 glycogen storage disease (debrancher deficiency, limit dextrinosis), tyrosinemia, tyrosinemia type 1, tyrosinemia type 2, tyrosinemia type 3, uridine diphosphate galactose 4-epimerase deficiency, urocanic aciduria, variegate porphyria, vitamin B12 deficiency, vitamin C toxicity, vitamin D deficiency, vitamin D-resistant rickets, vitamin d-sensitive rickets, vitamin E deficiency, vitamin E toxicity, vitamin K deficiency, vitamin K toxicity, von Gierke disease, Wernicke's encephalopathy, wet beriberi, Wilson's disease, xanthurenic aciduria, X-linked sideroblastic anemia, zinc deficiency, zinc toxicity, α -ketoadipic aciduria, α -methylacetoacetic aciduria, β -hydroxy- β -methylglutaric aciduria, β -methylcrotonyl glycinuria.

422. A mouse comprising a mutation in a gene encoding a polypeptide that is substantially identical to a polypeptide listed in Table 1.

423. The mouse of claim 422, wherein said mutation is a conditional mutation.

424. The mouse of claim 422, wherein said mutation comprises a deletion of all or a portion of said gene.

425. The mouse of claim 422, wherein said mutation comprises an insertion that disrupts the transcription of the RNA encoding said polypeptide or translation of said

polypeptide.

426. The mouse of claim 422, wherein said mutation comprises a point mutation.

427. The mouse of claim 422, wherein said mutation causes over expression of the gene.

428. The mouse of any of claims 422-427, wherein said mutation is in the coding region of said gene.

429. The mouse of any of claims 422-427, wherein said mutation is in the non-coding region of said gene.

430. The mouse of claim 422, wherein said mutation is a dominant-negative mutation.

431. A method of making a mouse exhibiting altered behavior, said method comprising the step of introducing into said mouse a mutation in a gene encoding a polypeptide comprising a polypeptide listed in any one of Tables 3-14 and 33.

432. The method of claim 431, wherein said mutation is a conditional mutation.

433. The method of claim 431, wherein said mutation comprises a deletion of all or a portion of said gene.

434. The method of claim 431, wherein said mutation comprises an insertion that disrupts the transcription of the RNA encoding said polypeptide or translation of said polypeptide.

435. The method of claim 431, wherein said mutation comprises a point mutation.

436. The method of claim 431, wherein said mutation is a dominant-negative mutation.

437. The method of claim 431, wherein said mutation causes over expression of the gene.

438. The method of any of claims 431-437, wherein said mutation is in the coding region of said gene.

439. The method of any of claims 431-437, wherein said mutation is in the non-coding region of said gene.

440. A cell isolated from a non-human mammal comprising a transgene comprising a nucleic acid molecule encoding a GPCR related polypeptide.

441. The cell of claim 440, wherein said non-human mammal is a mouse.

442. A cell isolated from a non-human mammal comprising a mutation in a gene encoding a polypeptide that is substantially identical to a polypeptide listed in Table 1.

443. The cell of claim 442, wherein said non-human mammal is a mouse.

444. The cell of claim 442, wherein said mutation is a conditional mutation.

445. The cell of claim 442, wherein said mutation comprises a deletion of all or a portion of said gene.

446. The mouse of claim 442, wherein said mutation comprises an insertion that disrupts the transcription of the RNA encoding said polypeptide or translation of said polypeptide.

447. The cell of claim 442, wherein said mutation comprises a point mutation.

448. The cell of any of claims 444-447, wherein said mutation is in the coding region of said gene.

449. The cell of any of claims 444-447, wherein said mutation is in the non-coding region of said gene.

450. The cell of claim 442, wherein said mutation is a dominant-negative mutation.

451. The cell of claim 442, wherein said mutation causes over expression of the gene.

452. A transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1.

453. The transgenic mouse of claim 452, wherein said transgene comprises a mutation.

454. The mouse of claim 453, wherein said mutation is a conditional mutation.

455. The mouse of claim 453, wherein said mutation comprises a deletion of all or a portion of said gene.

456. The mouse of claim 453, wherein said mutation comprises an insertion that disrupts the transcription of the RNA encoding said polypeptide or translation of said polypeptide.

457. The mouse of claim 453, wherein said mutation comprises a point

mutation.

458. The mouse of claim 453, wherein said mutation is a dominant-negative mutation.

459. The transgenic mouse of claim 452, wherein said transgene is overexpressed.

460. The transgenic mouse of claim 452, wherein said transgene is operably linked to an inducible promoter.

461. The transgenic mouse of claim 452, wherein said transgene is operably linked to a cell-type or tissue-specific promoter.

462. A transgenic mouse expressing a transgene encoding a mouse GPCR polypeptide listed in Table 1.

463. The transgenic mouse of claim 462, wherein said transgene comprises a mutation.

464. The mouse of claim 463, wherein said mutation is a conditional mutation.

465. The mouse of claim 463, wherein said mutation comprises a deletion of all or a portion of said gene.

466. The mouse of claim 463, wherein said mutation comprises an insertion that disrupts the transcription of the RNA encoding said polypeptide or translation of said polypeptide.

467. The mouse of claim 463, wherein said mutation comprises a point mutation.

468. The mouse of claim 463, wherein said mutation is a dominant-negative mutation.

469. The transgenic mouse of claim 462, wherein said transgene is overexpressed.

470. The transgenic mouse of any of claims 452-468, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

471. A cell derived from the transgenic mouse of any of claims 452-470.

472. A method for identifying a compound that may be useful for the treatment of a neurological disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in any one of Tables 3-14 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a neurological disease or disorder.

473. The method of claim 472, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

474. A method for identifying a compound that may be useful for the treatment of a neurological disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in one its neurological tissues a transgene encoding a human GPCR polypeptide listed in any one of Tables 3-14 and 33, said mouse having a neurological disease or disorder; and determining whether said candidate compound treats said neurological disease or disorder.

475. A method for identifying a compound that may be useful for the treatment of a neurological disease or disorder, said method comprising the steps of contacting a candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in any one of Tables 3-14 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a neurological disease or disorder.

476. The method of claim 475, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

477. A method for identifying a compound that may be useful for the treatment of a neurological disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 3-14 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a neurological disease or disorder.

478. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the adrenal gland, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 15 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the adrenal gland.

479. The method of claim 478, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

480. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the adrenal gland, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its adrenal gland a transgene encoding a human GPCR polypeptide listed in Tables 15 and 33, said mouse having a disease or disorder of the adrenal gland; and determining whether said candidate compound treats said disease or disorder of the adrenal gland.

481. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the adrenal gland, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 15 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the adrenal gland.

482. The method of claim 481, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

483. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the adrenal gland, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 15 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the adrenal gland.

484. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the colon, said method comprising the steps of administering

a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 16 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the colon.

485. The method of claim 484, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

486. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the colon, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its colon a transgene encoding a human GPCR polypeptide listed in Tables 16 and 33, said mouse having a disease or disorder of the colon; and determining whether said candidate compound treats said disease or disorder of the colon.

487. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the colon, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 16 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the colon.

488. The method of claim 487, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

489. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the colon, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR.

polypeptide listed in Tables 16 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the colon.

490. A method for identifying a compound that may be useful for the treatment of a cardiovascular disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 17 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a cardiovascular disease or disorder.

491. The method of claim 490, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

492. A method for identifying a compound that may be useful for the treatment of a cardiovascular disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its cardiovascular system a transgene encoding a human GPCR polypeptide listed in Tables 17 and 33, said mouse having a cardiovascular disease or disorder; and determining whether said candidate compound treats said cardiovascular disease or disorder.

493. A method for identifying a compound that may be useful for the treatment of a cardiovascular disease or disorder, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 17 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment

of a cardiovascular disease or disorder.

494. The method of claim 493, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

495. A method for identifying a compound that may be useful for the treatment of a cardiovascular disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 17 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease cardiovascular disease or disorder.

496. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the intestine, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 18 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the intestine.

497. The method of claim 496, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

498. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the intestine, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its intestine a transgene encoding a human GPCR polypeptide listed in Tables 18 and 33, said mouse having a disease or disorder of the intestine; and determining whether said candidate

compound treats said disease or disorder of the intestine.

499. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the intestine, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 18 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the intestine.

500. The method of claim 499, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

501. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the intestine, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 18 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the intestine.

502. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the kidney, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 19 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the kidney.

503. The method of claim 502, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

504. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the kidney, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its kidney a transgene encoding a human GPCR polypeptide listed in Tables 19 and 33, said mouse having a disease or disorder of the kidney; and determining whether said candidate compound treats said disease or disorder of the kidney.

505. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the kidney, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 19 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the kidney.

506. The method of claim 505, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

507. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the kidney, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 19 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the kidney.

508. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the liver, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 20 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the liver.

509. The method of claim 508, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

510. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the liver, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its liver a transgene encoding a human GPCR polypeptide listed in Tables 20 and 33, said mouse having a disease or disorder of the liver; and determining whether said candidate compound treats said disease or disorder of the liver.

511. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the liver, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 20 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the liver.

512. The method of claim 511, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

513. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the liver, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 20 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the liver.

514. A method for identifying a compound that may be useful for the treatment of a lung disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 21 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a lung disease or disorder.

515. The method of claim 514, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

516. A method for identifying a compound that may be useful for the treatment of a lung disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its lung a transgene encoding a human GPCR polypeptide listed in Tables 21 and 33, said mouse having a lung disease or disorder; and determining whether said candidate compound treats said lung disease or disorder.

517. A method for identifying a compound that may be useful for the treatment of a lung disease or disorder, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 21 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration

in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a lung disease or disorder.

518. The method of claim 517, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

519. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the lung, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 21 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the lung.

520. A method for identifying a compound that may be useful for the treatment of a muscular disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 22 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a muscular disease or disorder.

521. The method of claim 520, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

522. A method for identifying a compound that may be useful for the treatment of a muscular disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its muscular tissue a transgene encoding a human GPCR polypeptide listed in Tables 22 and 33, said mouse having a muscular disease or disorder; and determining whether said candidate compound treats said muscular disease or disorder.

523. A method for identifying a compound that may be useful for the treatment of a muscular disease or disorder, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 22 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a muscular disease or disorder.

524. The method of claim 523, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

525. A method for identifying a compound that may be useful for the treatment of a muscular disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 22 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a muscular disease or disorder.

526. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the ovary, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 23 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the ovary.

527. The method of claim 526, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

528. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the ovary, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its ovary a transgene encoding a human GPCR polypeptide listed in Tables 23 and 33, said mouse having a disease or disorder of the ovary; and determining whether said candidate compound treats said disease or disorder of the ovary.

529. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the ovary, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 23 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the ovary.

530. The method of claim 529, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

531. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the ovary, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 23 and 33 and 531; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the ovary.

532. A method for identifying a compound that may be useful for the treatment of a blood disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human

GPCR polypeptide listed in Tables 24 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a blood disease or disorder.

533. The method of claim 532, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

534. A method for identifying a compound that may be useful for the treatment of a blood disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its peripheral blood lymphocytes a transgene encoding a human GPCR polypeptide listed in Tables 24 and 33, said mouse having a blood disease or disorder; and determining whether said candidate compound treats said blood disease or disorder.

535. A method for identifying a compound that may be useful for the treatment of a blood disease or disorder, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 24 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a blood disease or disorder.

536. The method of claim 535, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

537. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the blood, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 24 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration

in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the blood.

538. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the prostate, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 25 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the prostate.

539. The method of claim 538, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

540. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the prostate, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its prostate a transgene encoding a human GPCR polypeptide listed in Tables 25 and 33, said mouse having a disease or disorder of the prostate; and determining whether said candidate compound treats said disease or disorder of the prostate.

541. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the prostate, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 25 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the prostate.

542. The method of claim 541, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

543. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the prostate said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 25 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the prostate.

544. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the skin, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 26 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the skin.

545. The method of claim 544, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

546. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the skin, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its skin a transgene encoding a human GPCR polypeptide listed in Tables 26 and 33, said mouse having a disease or disorder of the skin; and determining whether said candidate compound treats said disease or disorder of the skin.

547. A method for identifying a compound that may be useful for the treatment

of a disease or disorder of the skin, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 26 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the skin.

548. The method of claim 547, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

549. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the skin, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 26 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the skin.

550. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the spleen, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 27 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the spleen.

551. The method of claim 550, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

552. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the spleen, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its spleen a transgene encoding a human GPCR polypeptide listed in Tables 27 and 33, said mouse having a disease or disorder of the spleen; and determining whether said candidate compound treats said disease or disorder of the spleen.

553. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the spleen, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 27 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the spleen.

554. The method of claim 553, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

555. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the spleen, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 27 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the spleen.

556. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the stomach, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene

encoding a human GPCR polypeptide listed in Tables 28 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the stomach.

557. The method of claim 556 wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

558. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the stomach, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its stomach a transgene encoding a human GPCR polypeptide listed in Tables 28 and 33, said mouse having a disease or disorder of the stomach; and determining whether said candidate compound treats said disease or disorder of the stomach.

559. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the stomach, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 28 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the stomach.

560. The method of claim 559, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

561. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the stomach, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a

GPCR polypeptide listed in Tables 28 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the stomach.

562. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the testes, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 29 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the testes.

563. The method of claim 562, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

564. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the testes, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its testes a transgene encoding a human GPCR polypeptide listed in Tables 29 and 33, said mouse having a disease or disorder of the testes; and determining whether said candidate compound treats said disease or disorder of the testes.

565. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the testes, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 29 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment

of a disease or disorder of the testes.

566. The method of claim 565, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

567. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the testes, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 29 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the testes.

568. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thymus, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 30 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the thymus.

569. The method of claim 568, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

570. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thymus, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its thymus a transgene encoding a human GPCR polypeptide listed in Tables 30 and 33, said mouse having a disease or disorder of the thymus; and determining whether said candidate compound treats said disease or disorder of the thymus.

571. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thymus, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 30 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the thymus.

572. The method of claim 571, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

573. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thymus, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 30 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the thymus.

574. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thyroid, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 31 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the thyroid.

575. The method of claim 574, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

576. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thyroid, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its thyroid a transgene encoding a human GPCR polypeptide listed in Tables 31 and 33, said mouse having a disease or disorder of the thyroid; and determining whether said candidate compound treats said disease or disorder of the thyroid.

577. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thyroid, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 31 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the thyroid.

578. The method of claim 577, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

579. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the thyroid, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 31 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the thyroid.

580. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the uterus, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 32 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the uterus.

581. The method of claim 580, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

582. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the uterus, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its uterus a transgene encoding a human GPCR polypeptide listed in Tables 32 and 33, said mouse having a disease or disorder of the uterus; and determining whether said candidate compound treats said disease or disorder of the uterus.

583. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the uterus, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Tables 32 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the uterus.

584. The method of claim 583, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

585. A method for identifying a compound that may be useful for the treatment

of a disease or disorder of the uterus, said method comprising the steps of administering a candidate compound to a transgenic mouse comprising a mutation in a GPCR polypeptide listed in Tables 32 and 33; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein an alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the uterus.

586. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the pancreas, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the pancreas.

587. The method of claim 586, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

588. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the pancreas, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its pancreas a transgene encoding a human GPCR polypeptide listed in Table 1, said mouse having a disease or disorder of the pancreas; and determining whether said candidate compound treats said disease or disorder of the pancreas.

589. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the pancreas, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a

alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the pancreas.

590. The method of claim 589, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

591. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the bone and joints, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the bone and joints.

592. The method of claim 591, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

593. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the bone and joints, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its bone and joints a transgene encoding a human GPCR polypeptide listed in Table 1, said mouse having a disease or disorder of the bone and joints; and determining whether said candidate compound treats said disease or disorder of the bone and joints.

594. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the bone and joints, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR

polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the bone and joints.

595. The method of claim 594, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

596. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the breast, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the breast.

597. The method of claim 596, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

598. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the breast, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its breast a transgene encoding a human GPCR polypeptide listed in Table 1, said mouse having a disease or disorder of the breast; and determining whether said candidate compound treats said disease or disorder of the breast.

599. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the breast, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate

compound as a compound that may be useful for the treatment of a disease or disorder of the breast.

600. The method of claim 599, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

601. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the immune system, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the immune system.

602. The method of claim 601, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

603. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the immune system, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing in its immune system a transgene encoding a human GPCR polypeptide listed in Table 1, said mouse having a disease or disorder of the immune system; and determining whether said candidate compound treats said disease or disorder of the immune system.

604. A method for identifying a compound that may be useful for the treatment of a disease or disorder of the immune system, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide

identifies said candidate compound as a compound that may be useful for the treatment of a disease or disorder of the immune system.

605. The method of claim 604, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

606. A method for identifying a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide identifies said candidate compound as a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder.

607. The method of claim 606, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

608. A method for identifying a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder, said method comprising the steps of administering a candidate compound to a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1, said mouse having a metabolic or nutritive disease or disorder; and determining whether said candidate compound treats said metabolic or nutritive disease or disorder.

609. A method for identifying a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder, said method comprising the steps of contacting candidate compound with a cell from a transgenic mouse expressing a transgene encoding a human GPCR polypeptide listed in Table 1; and determining whether said candidate compound alters the biological activity of said GPCR polypeptide, wherein a alteration in the biological activity of said GPCR polypeptide

identifies said candidate compound as a compound that may be useful for the treatment of a metabolic or nutritive disease or disorder.

610. The method of claim 609, wherein said mouse has a mutation in the endogenous gene that is orthologous to said transgene.

611. The method of any one of claims 253-258, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said neurological disease or disorder.

612. The method of any one of claims 259-264, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the adrenal gland.

613. The method of any one of claims 265-270, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the colon.

614. The method of any one of claims 271-276, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said cardiovascular disease or disorder.

615. The method of any one of claims 277-282, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the intestine.

616. The method of any one of claims 283-288, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the kidney.

617. The method of any one of claims 289-294, further comprising the step of

testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the liver.

618. The method of any one of claims 295-300, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said lung disease or disorder.

619. The method of any one of claims 301-306, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said muscular disease or disorder.

620. The method of any one of claims 307-312, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the ovary.

621. The method of any one of claims 313-318, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said blood disease or disorder.

622. The method of any one of claims 319-324, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the prostate.

623. The method of any one of claims 325-330, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the skin.

624. The method of any one of claims 331-336, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the spleen.

625. The method of any one of claims 337-342, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the stomach.

626. The method of any one of claims 343-348, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the testes.

627. The method of any one of claims 349-354, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the thymus.

628. The method of any one of claims 355-360, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the thyroid.

629. The method of any one of claims 361-366, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the uterus.

630. The method of any one of claims 367-372, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the pancreas.

631. The method of any one of claims 373-378, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the bone and joints.

632. The method of any one of claims 379-384, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the breast.

633. The method of any one of claims 385-390, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said disease or disorder of the immune system.

634. The method of any one of claims 391-396, further comprising the step of testing said identified candidate compound in a cell- or animal-based model for said metabolic or nutritive disease or disorder.

635. A kit comprising a plurality of polynucleotides, wherein each polynucleotide hybridizes under high stringency conditions to a GPCR polynucleotide of Table 1, wherein at least 50 different polynucleotides, each capable of hybridizing under high stringency conditions to a different human GPCR polynucleotide listed on Table 1, are present in said kit.

636. A kit comprising a plurality of polynucleotides, wherein polynucleotides that hybridize under high stringency conditions, each each to a different GPCR polynucleotide listed on one of Tables 3-14 and 33, are present in said kit such that said kit comprises polynucleotides that collectively hybridize to each of said GPCR polynucleotides listed on one of Tables 3-14 and 33.

637. A kit comprising a plurality of polynucleotides, wherein polynucleotides that hybridize under high stringency conditions, each each to a different GPCR polynucleotide listed on one of Tables 15-32, are present in said kit such that said kit comprises polynucleotides that collectively hybridize to each of said GPCR polynucleotides listed on one of Tables 15-32.

638. A kit comprising a plurality of mice, each mouse having a mutation in a GPCR polynucleotide of Table 1, wherein at least 50 mice, each having a mutation in a different GPCR polynucleotide listed on Table 1, are present in said kit.

639. The kit of claim 638, further comprising a plurality of polynucleotides, wherein each polynucleotide hybridizes under high stringency conditions to a GPCR polynucleotide of Table 1, wherein at least 50 different polynucleotides, each capable of hybridizing under high stringency conditions to a different mouse GPCR polynucleotide listed on Table 1, are present in said kit.

640. A kit comprising a plurality of mice, each mouse having a mutation in a GPCR polynucleotide, wherein, collectively, mice having a mutation in each GPCR polynucleotide listed on one of Tables 3-14 and 33 are present in said kit.

641. A kit comprising a plurality of mice, each mouse having a mutation in a GPCR polynucleotide, wherein, collectively, mice having a mutation in each GPCR polynucleotide listed on one of Tables 15-32 are present in said kit.

642. The kit of any one of claims 635-641, wherein at least one of said GPCR polynucleotides is a GPCR polynucleotide of Table 2.

FIGURE 1.

esoGPCR Genes

| Class A | | | | Class A | | | | Class A | | | | Class A | | | | Class B | | | |
|-------------------------------|---------|-------------|---------|-------------------------------|---------|-------------|---------|-------------------------------|---------|-------------|---------|------------------|-------|-------------|---------|---------------------|-------|-------------|---------|
| Family | Gene | Database ID | Species | Family | Gene | Database ID | Species | Family | Gene | Database ID | Species | Family | Gene | Database ID | Species | Family | Gene | Database ID | Species |
| Acetylcholine (muscarinic) | CHRM1 | 81 | H.M. | Muscarinic | MHR1 | 857 | H.M. | Postopitoid | PTGDR | 872 | H.M. | Orphan group A6 | OPR4 | 828 | H.M. | Parathyroid hormone | PDR1 | 838 | H.M. |
| | CHRM2 | 1 | H.M. | | MHR2 | 88 | H.M. | | PTGER1 | 873 | H.M. | | OPR5 | 238 | H.M. | | PDR2 | 351 | H.M. |
| | CHRM3 | 3 | H.M. | | MHR3 | 88 | H.M. | | PTGER2 | 874 | H.M. | | OPR6 | 240 | H.M. | | PDR3 | 352 | H.M. |
| | CHRM4 | 4 | H.M. | | MHR4 | 89 | H.M. | | PTGER3 | 875 | H.M. | | OPR7 | 241 | H.M. | | PDR4 | 353 | H.M. |
| Adenosine | ADORA1 | 8 | H.M. | Adenosine | ADORA1 | 8 | H.M. | Adenosine | ADORA1 | 8 | H.M. | Orphan group A8 | OPR8 | 242 | H.M. | Orphan group A9 | OPR9 | 243 | H.M. |
| | ADORA2A | 7 | H.M. | | ADORA2A | 7 | H.M. | | ADORA2A | 7 | H.M. | | OPR10 | 244 | H.M. | | OPR10 | 244 | H.M. |
| | ADORA2B | 9 | H.M. | | ADORA2B | 9 | H.M. | | ADORA2B | 9 | H.M. | | OPR11 | 245 | H.M. | | OPR11 | 245 | H.M. |
| | ADORA3 | 8 | H.M. | | ADORA3 | 8 | H.M. | | ADORA3 | 8 | H.M. | | OPR12 | 246 | H.M. | | OPR12 | 246 | H.M. |
| ADP-ribose | ADPR1 | 10 | H.M. | ADP-ribose | ADPR1 | 10 | H.M. | ADP-ribose | ADPR1 | 10 | H.M. | Orphan group A10 | OPR13 | 247 | H.M. | Orphan group A11 | OPR14 | 248 | H.M. |
| | ADPR2 | 11 | H.M. | | ADPR2 | 11 | H.M. | | ADPR2 | 11 | H.M. | | OPR15 | 249 | H.M. | | OPR15 | 249 | H.M. |
| | ADPR3 | 12 | H.M. | | ADPR3 | 12 | H.M. | | ADPR3 | 12 | H.M. | | OPR16 | 250 | H.M. | | OPR16 | 250 | H.M. |
| | ADPR4 | 13 | H.M. | | ADPR4 | 13 | H.M. | | ADPR4 | 13 | H.M. | | OPR17 | 251 | H.M. | | OPR17 | 251 | H.M. |
| Adrenocortical | ADRA1 | 14 | H.M. | Adrenocortical | ADRA1 | 14 | H.M. | Adrenocortical | ADRA1 | 14 | H.M. | Orphan group A12 | OPR18 | 252 | H.M. | Orphan group A13 | OPR19 | 253 | H.M. |
| | ADRA2 | 15 | H.M. | | ADRA2 | 15 | H.M. | | ADRA2 | 15 | H.M. | | OPR20 | 254 | H.M. | | OPR20 | 254 | H.M. |
| | ADRA3 | 16 | H.M. | | ADRA3 | 16 | H.M. | | ADRA3 | 16 | H.M. | | OPR21 | 255 | H.M. | | OPR21 | 255 | H.M. |
| | ADRA4 | 17 | H.M. | | ADRA4 | 17 | H.M. | | ADRA4 | 17 | H.M. | | OPR22 | 256 | H.M. | | OPR22 | 256 | H.M. |
| Angiotensin | ANG1 | 18 | H.M. | Angiotensin | ANG1 | 18 | H.M. | Angiotensin | ANG1 | 18 | H.M. | Orphan group A14 | OPR23 | 257 | H.M. | Orphan group A15 | OPR24 | 258 | H.M. |
| | ANG2 | 19 | H.M. | | ANG2 | 19 | H.M. | | ANG2 | 19 | H.M. | | OPR25 | 259 | H.M. | | OPR25 | 259 | H.M. |
| | ANG3 | 20 | H.M. | | ANG3 | 20 | H.M. | | ANG3 | 20 | H.M. | | OPR26 | 260 | H.M. | | OPR26 | 260 | H.M. |
| | ANG4 | 21 | H.M. | | ANG4 | 21 | H.M. | | ANG4 | 21 | H.M. | | OPR27 | 261 | H.M. | | OPR27 | 261 | H.M. |
| Anaphylaxis | ANA1 | 22 | H.M. | Anaphylaxis | ANA1 | 22 | H.M. | Anaphylaxis | ANA1 | 22 | H.M. | Orphan group A16 | OPR28 | 262 | H.M. | Orphan group A17 | OPR29 | 263 | H.M. |
| | ANA2 | 23 | H.M. | | ANA2 | 23 | H.M. | | ANA2 | 23 | H.M. | | OPR30 | 264 | H.M. | | OPR30 | 264 | H.M. |
| | ANA3 | 24 | H.M. | | ANA3 | 24 | H.M. | | ANA3 | 24 | H.M. | | OPR31 | 265 | H.M. | | OPR31 | 265 | H.M. |
| | ANA4 | 25 | H.M. | | ANA4 | 25 | H.M. | | ANA4 | 25 | H.M. | | OPR32 | 266 | H.M. | | OPR32 | 266 | H.M. |
| Apolipoprotein | APOL1 | 26 | H.M. | Apolipoprotein | APOL1 | 26 | H.M. | Apolipoprotein | APOL1 | 26 | H.M. | Orphan group A18 | OPR33 | 267 | H.M. | Orphan group A19 | OPR34 | 268 | H.M. |
| | APOL2 | 27 | H.M. | | APOL2 | 27 | H.M. | | APOL2 | 27 | H.M. | | OPR35 | 269 | H.M. | | OPR35 | 269 | H.M. |
| | APOL3 | 28 | H.M. | | APOL3 | 28 | H.M. | | APOL3 | 28 | H.M. | | OPR36 | 270 | H.M. | | OPR36 | 270 | H.M. |
| | APOL4 | 29 | H.M. | | APOL4 | 29 | H.M. | | APOL4 | 29 | H.M. | | OPR37 | 271 | H.M. | | OPR37 | 271 | H.M. |
| Arachidonic | ARA1 | 30 | H.M. | Arachidonic | ARA1 | 30 | H.M. | Arachidonic | ARA1 | 30 | H.M. | Orphan group A20 | OPR38 | 272 | H.M. | Orphan group A21 | OPR39 | 273 | H.M. |
| | ARA2 | 31 | H.M. | | ARA2 | 31 | H.M. | | ARA2 | 31 | H.M. | | OPR40 | 274 | H.M. | | OPR40 | 274 | H.M. |
| | ARA3 | 32 | H.M. | | ARA3 | 32 | H.M. | | ARA3 | 32 | H.M. | | OPR41 | 275 | H.M. | | OPR41 | 275 | H.M. |
| | ARA4 | 33 | H.M. | | ARA4 | 33 | H.M. | | ARA4 | 33 | H.M. | | OPR42 | 276 | H.M. | | OPR42 | 276 | H.M. |
| Bile acid | BIL1 | 34 | H.M. | Bile acid | BIL1 | 34 | H.M. | Bile acid | BIL1 | 34 | H.M. | Orphan group A22 | OPR43 | 277 | H.M. | Orphan group A23 | OPR44 | 278 | H.M. |
| | BIL2 | 35 | H.M. | | BIL2 | 35 | H.M. | | BIL2 | 35 | H.M. | | OPR45 | 279 | H.M. | | OPR45 | 279 | H.M. |
| | BIL3 | 36 | H.M. | | BIL3 | 36 | H.M. | | BIL3 | 36 | H.M. | | OPR46 | 280 | H.M. | | OPR46 | 280 | H.M. |
| | BIL4 | 37 | H.M. | | BIL4 | 37 | H.M. | | BIL4 | 37 | H.M. | | OPR47 | 281 | H.M. | | OPR47 | 281 | H.M. |
| Calcitonin | CAL1 | 38 | H.M. | Calcitonin | CAL1 | 38 | H.M. | Calcitonin | CAL1 | 38 | H.M. | Orphan group A24 | OPR48 | 282 | H.M. | Orphan group A25 | OPR49 | 283 | H.M. |
| | CAL2 | 39 | H.M. | | CAL2 | 39 | H.M. | | CAL2 | 39 | H.M. | | OPR50 | 284 | H.M. | | OPR50 | 284 | H.M. |
| | CAL3 | 40 | H.M. | | CAL3 | 40 | H.M. | | CAL3 | 40 | H.M. | | OPR51 | 285 | H.M. | | OPR51 | 285 | H.M. |
| | CAL4 | 41 | H.M. | | CAL4 | 41 | H.M. | | CAL4 | 41 | H.M. | | OPR52 | 286 | H.M. | | OPR52 | 286 | H.M. |
| Calcitonin receptor | CALR1 | 42 | H.M. | Calcitonin receptor | CALR1 | 42 | H.M. | Calcitonin receptor | CALR1 | 42 | H.M. | Orphan group A26 | OPR53 | 287 | H.M. | Orphan group A27 | OPR54 | 288 | H.M. |
| | CALR2 | 43 | H.M. | | CALR2 | 43 | H.M. | | CALR2 | 43 | H.M. | | OPR55 | 289 | H.M. | | OPR55 | 289 | H.M. |
| | CALR3 | 44 | H.M. | | CALR3 | 44 | H.M. | | CALR3 | 44 | H.M. | | OPR56 | 290 | H.M. | | OPR56 | 290 | H.M. |
| | CALR4 | 45 | H.M. | | CALR4 | 45 | H.M. | | CALR4 | 45 | H.M. | | OPR57 | 291 | H.M. | | OPR57 | 291 | H.M. |
| Calcitonin receptor-like | CALRL1 | 46 | H.M. | Calcitonin receptor-like | CALRL1 | 46 | H.M. | Calcitonin receptor-like | CALRL1 | 46 | H.M. | Orphan group A28 | OPR58 | 292 | H.M. | Orphan group A29 | OPR59 | 293 | H.M. |
| | CALRL2 | 47 | H.M. | | CALRL2 | 47 | H.M. | | CALRL2 | 47 | H.M. | | OPR60 | 294 | H.M. | | OPR60 | 294 | H.M. |
| | CALRL3 | 48 | H.M. | | CALRL3 | 48 | H.M. | | CALRL3 | 48 | H.M. | | OPR61 | 295 | H.M. | | OPR61 | 295 | H.M. |
| | CALRL4 | 49 | H.M. | | CALRL4 | 49 | H.M. | | CALRL4 | 49 | H.M. | | OPR62 | 296 | H.M. | | OPR62 | 296 | H.M. |
| Calcitonin receptor-related | CALRLR1 | 50 | H.M. | Calcitonin receptor-related | CALRLR1 | 50 | H.M. | Calcitonin receptor-related | CALRLR1 | 50 | H.M. | Orphan group A30 | OPR63 | 297 | H.M. | Orphan group A31 | OPR64 | 298 | H.M. |
| | CALRLR2 | 51 | H.M. | | CALRLR2 | 51 | H.M. | | CALRLR2 | 51 | H.M. | | OPR65 | 299 | H.M. | | OPR65 | 299 | H.M. |
| | CALRLR3 | 52 | H.M. | | CALRLR3 | 52 | H.M. | | CALRLR3 | 52 | H.M. | | OPR66 | 300 | H.M. | | OPR66 | 300 | H.M. |
| | CALRLR4 | 53 | H.M. | | CALRLR4 | 53 | H.M. | | CALRLR4 | 53 | H.M. | | OPR67 | 301 | H.M. | | OPR67 | 301 | H.M. |
| Calcitonin receptor-related 2 | CALRLR2 | 54 | H.M. | Calcitonin receptor-related 2 | CALRLR2 | 54 | H.M. | Calcitonin receptor-related 2 | CALRLR2 | 54 | H.M. | Orphan group A32 | OPR68 | 302 | H.M. | Orphan group A33 | OPR69 | 303 | H.M. |
| | CALRLR3 | 55 | H.M. | | CALRLR3 | 55 | H.M. | | CALRLR3 | 55 | H.M. | | OPR70 | 304 | H.M. | | OPR70 | 304 | H.M. |
| | CALRLR4 | 56 | H.M. | | CALRLR4 | 56 | H.M. | | CALRLR4 | 56 | H.M. | | OPR71 | 305 | H.M. | | OPR71 | 305 | H.M. |
| | CALRLR5 | 57 | H.M. | | CALRLR5 | 57 | H.M. | | CALRLR5 | 57 | H.M. | | OPR72 | 306 | H.M. | | OPR72 | 306 | H.M. |
| Calcitonin receptor-related 3 | CALRLR3 | 58 | H.M. | Calcitonin receptor-related 3 | CALRLR3 | 58 | H.M. | Calcitonin receptor-related 3 | CALRLR3 | 58 | H.M. | Orphan group A34 | OPR73 | 307 | H.M. | Orphan group A35 | OPR74 | 308 | H.M. |
| | CALRLR4 | 59 | H.M. | | CALRLR4 | 59 | H.M. | | CALRLR4 | 59 | H.M. | | OPR75 | 309 | H.M. | | OPR75 | 309 | H.M. |
| | CALRLR5 | 60 | H.M. | | CALRLR5 | 60 | H.M. | | CALRLR5 | 60 | H.M. | | OPR76 | 310 | H.M. | | OPR76 | 310 | H.M. |
| | CALRLR6 | 61 | H.M. | | CALRLR6 | 61 | H.M. | | CALRLR6 | 61 | H.M. | | OPR77 | 311 | H.M. | | OPR77 | 311 | H.M. |
| Calcitonin receptor-related 4 | CALRLR4 | 62 | H.M. | Calcitonin receptor-related 4 | CALRLR4 | 62 | H.M. | Calcitonin receptor-related 4 | CALRLR4 | 62 | H.M. | Orphan group A36 | OPR78 | 312 | H.M. | Orphan group A37 | OPR79 | 313 | H.M. |
| | CALRLR5 | 63 | H.M. | | CALRLR5 | 63 | H.M. | | CALRLR5 | 63 | H.M. | | OPR80 | 314 | H.M. | | OPR80 | 314 | H.M. |
| | CALRLR6 | 64 | H.M. | | CALRLR6 | 64 | H.M. | | CALRLR6 | 64 | H.M. | | OPR81 | 315 | H.M. | | OPR81 | 315 | H.M. |
| | CALRLR7 | 65 | H.M. | | CALRLR7 | 65 | H.M. | | CALRLR7 | 65 | H.M. | | OPR82 | 316 | H.M. | | OPR82 | 316 | H.M. |
| Calcitonin receptor-related 5 | CALRLR5 | 66 | H.M. | Calcitonin receptor-related 5 | CALRLR5 | 66 | H.M. | Calcitonin receptor-related 5 | CALRLR5 | 66 | H.M. | Orphan group A38 | OPR83 | 317 | H.M. | Orphan group A39 | OPR84 | 318 | H.M. |
| | CALRLR6 | 67 | H.M. | | CALRLR6 | 67 | H.M. | | CALRLR6 | 67 | H.M. | | OPR85 | 319 | H.M. | | OPR85 | 319 | H.M. |
| | CALRLR7 | 68 | H.M. | | CALRLR7 | 68 | H.M. | | CALRLR7 | 68 | H.M. | | OPR86 | 320 | H.M. | | OPR86 | 320 | H.M. |
| | CALRLR8 | 69 | H.M. | | CALRLR8 | 69 | H.M. | | CALRLR8 | 69 | H.M. | | OPR87 | 321 | H.M. | | OPR87 | 321 | H.M. |
| Calcitonin receptor-related 6 | CALRLR6 | 70 | H.M. | Calcitonin receptor-related 6 | CALRLR6 | 70 | H.M. | Calcitonin receptor-related 6 | CALRLR6 | 70 | H.M. | Orphan group A40 | OPR88 | 322 | H.M. | Orphan group A41 | OPR89 | 323 | H.M. |
| | CALRLR7 | 71 | H.M. | | | | | | | | | | | | | | | | |

FIGURE 2.

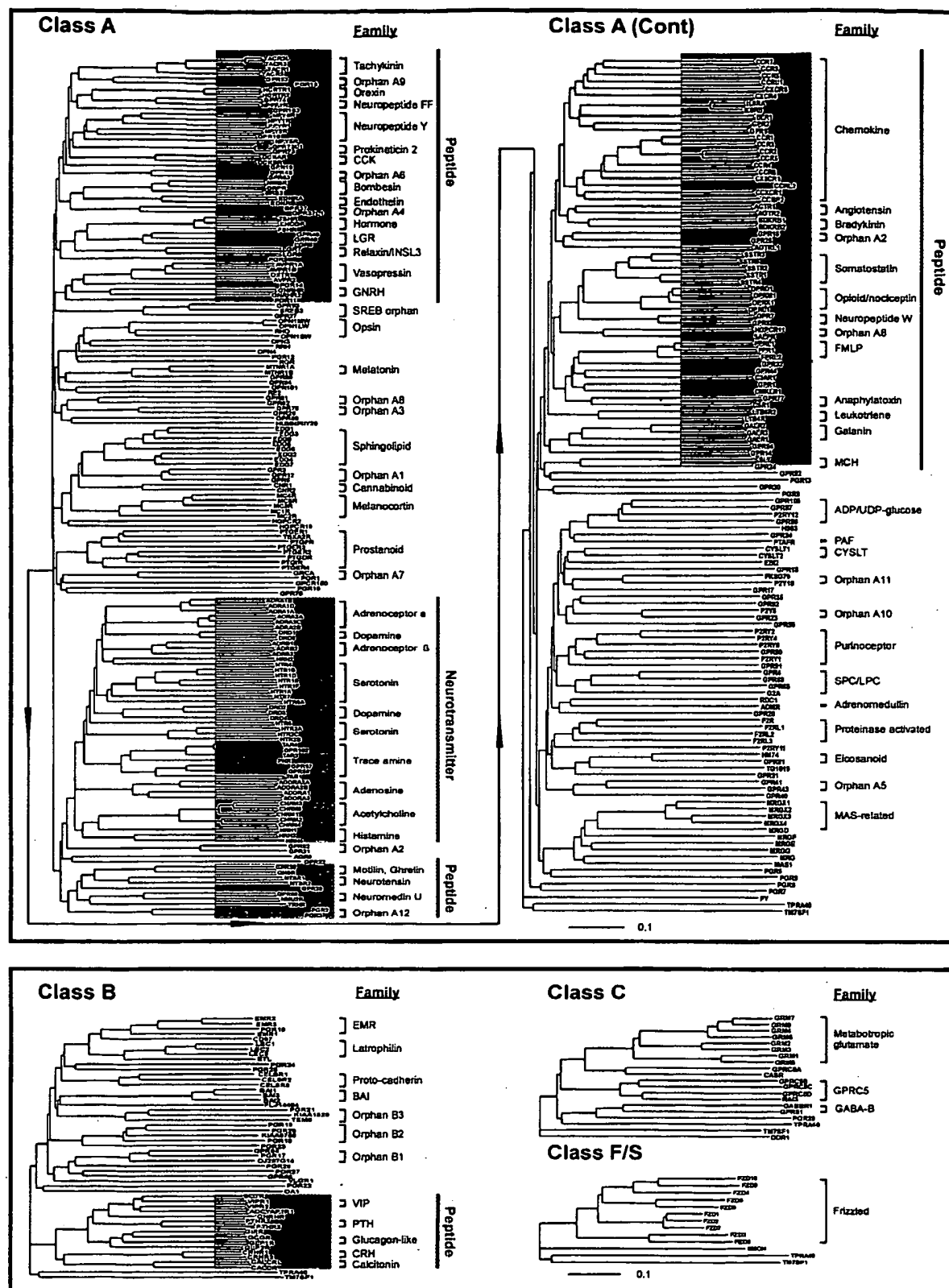


FIGURE 3.

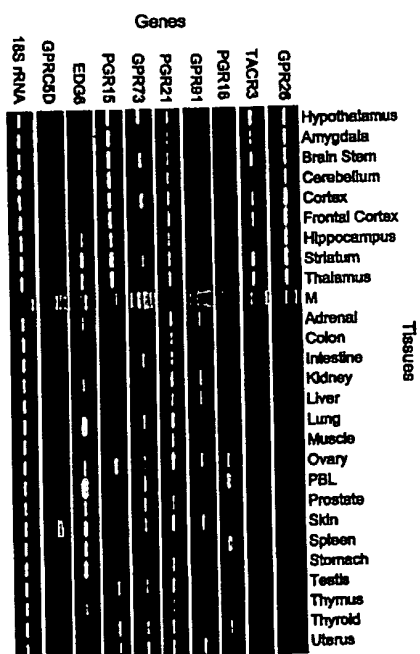


FIGURE 4.

| Tissues | Genes |
|----------------|----------|
| Hypothalamus | MRGG |
| Hypocampus | GPR01 |
| Brainstem | GPRC5D |
| Cerebellum | HM74 |
| Cortex | CYSLT2 |
| Frontal Cortex | PGR17 |
| Hippocampus | GPR9 |
| Striatum | IL8RA |
| Nucleus | CCR3 |
| Adipose | P2Y10 |
| Colon | PGR27 |
| Intestine | AGTRL1 |
| Kidney | EDG8 |
| Liver | GPR101 |
| Lung | GPR88 |
| Muscle | SREB3 |
| Myeloid | GALR2 |
| Pituitary | PGR8 |
| Pituitary | TACR3 |
| Pituitary | BAI1 |
| Pituitary | NTSR1 |
| Pituitary | GPR85 |
| Pituitary | GPR12 |
| Pituitary | HRH3 |
| Pituitary | GPR37L1 |
| Pituitary | GPR26 |
| Pituitary | HTR7 |
| Pituitary | HTR1F |
| Pituitary | GPR17 |
| Pituitary | GPR77 |
| Pituitary | GPR75 |
| Pituitary | GPR63 |
| Pituitary | HTR2A |
| Pituitary | PGR7 |
| Pituitary | CELSR2 |
| Pituitary | CELSR3 |
| Pituitary | GPR86 |
| Pituitary | GRCA |
| Pituitary | PGR19 |
| Pituitary | PGR15 |
| Pituitary | HTR4 |
| Pituitary | GPR37 |
| Pituitary | RE2 |
| Pituitary | LEC3 |
| Pituitary | LEC1 |
| Pituitary | LEC2 |
| Pituitary | P2RY12 |
| Pituitary | GPR19 |
| Pituitary | EDG8 |
| Pituitary | GPR23 |
| Pituitary | GPRC5B |
| Pituitary | HTR1D |
| Pituitary | TRHR2 |
| Pituitary | GPR4 |
| Pituitary | TM7SF3 |
| Pituitary | PGR23 |
| Pituitary | GPR105 |
| Pituitary | CD97 |
| Pituitary | CMKLR1 |
| Pituitary | KIAA0758 |
| Pituitary | PGR22 |
| Pituitary | TM7SF1 |
| Pituitary | GPR22 |
| Pituitary | TPRA40 |
| Pituitary | P2Y5 |
| Pituitary | RDC1 |
| Pituitary | GPR73 |
| Pituitary | GPR80 |
| Pituitary | CCSF2 |
| Pituitary | P2RY6 |
| Pituitary | CCRL1 |
| Pituitary | GPR48 |
| Pituitary | GPR21 |
| Pituitary | MRGF |
| Pituitary | GPR43 |
| Pituitary | H063 |
| Pituitary | GPR82 |
| Pituitary | CYSLT1 |
| Pituitary | ETL |
| Pituitary | TEM5 |
| Pituitary | GPR82 |
| Pituitary | CXCR6 |
| Pituitary | GPR18 |
| Pituitary | GPR84 |
| Pituitary | VIPR2 |
| Pituitary | GPR66 |
| Pituitary | GPR55 |
| Pituitary | EMR1 |
| Pituitary | GPRC5C |
| Pituitary | FKSG70 |
| Pituitary | HGPCR11 |
| Pituitary | PGR29 |
| Pituitary | LGR6 |
| Pituitary | PTGDR |
| Pituitary | GPR31 |
| Pituitary | FPR-SS2 |
| Pituitary | GPR35 |
| Pituitary | PGR10 |
| Pituitary | HCTR1 |
| Pituitary | SSTR3 |

FIGURE 5.

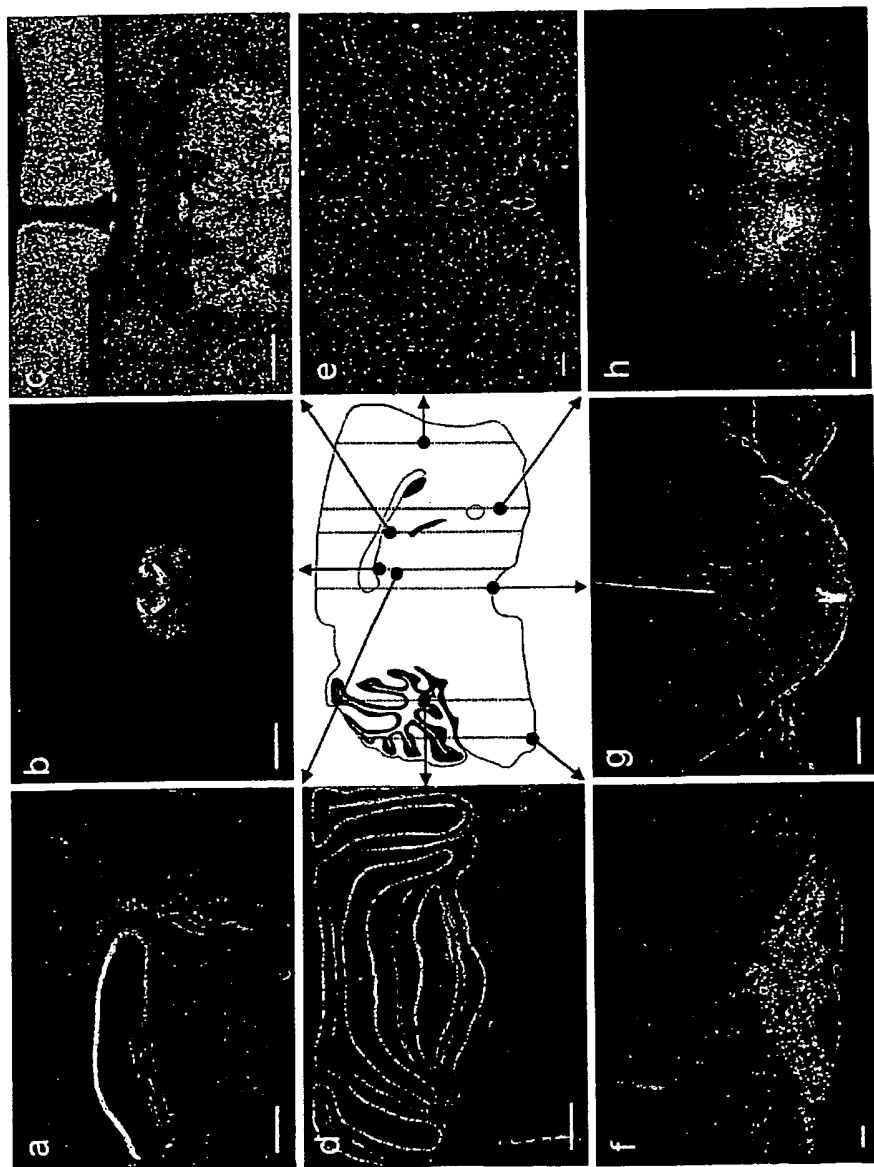


FIGURE 6A.

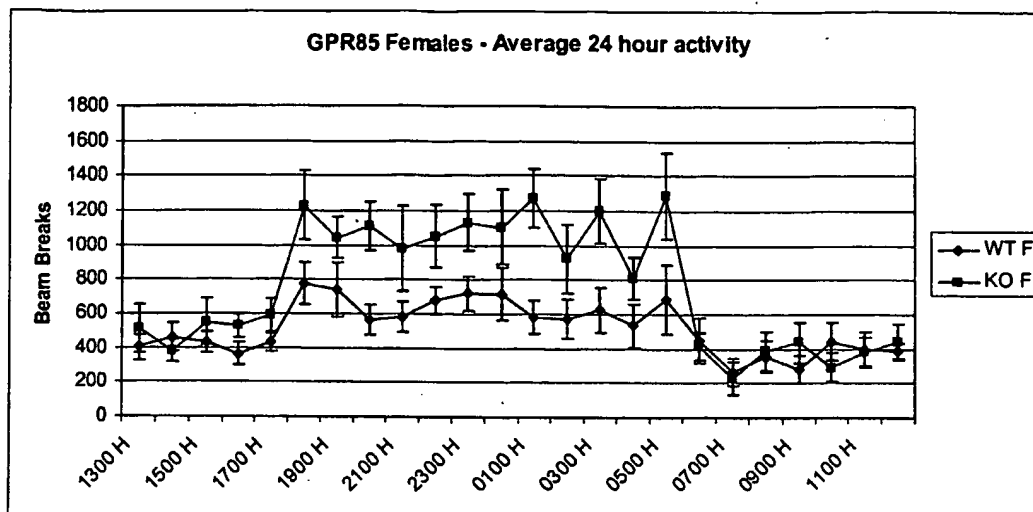


FIGURE 6B.

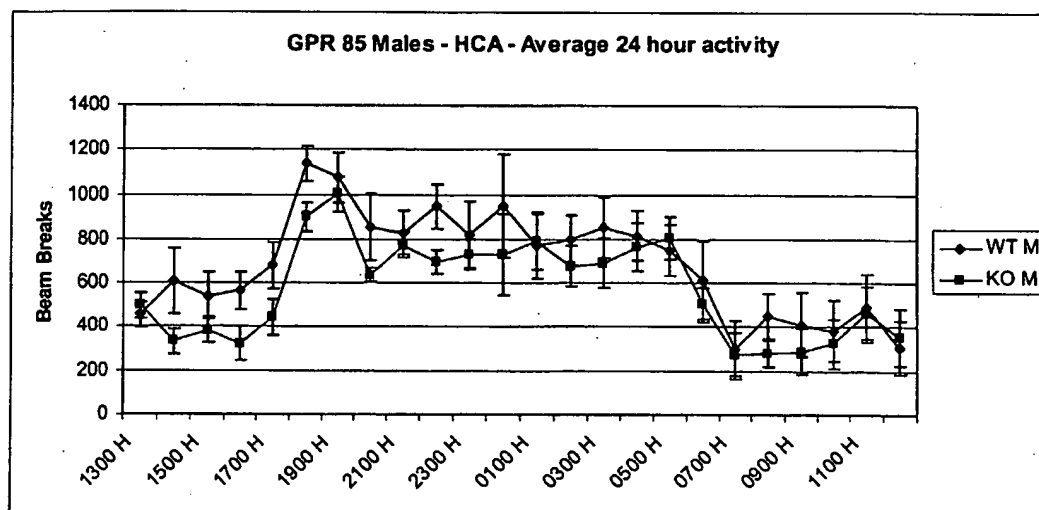


FIGURE 7A.

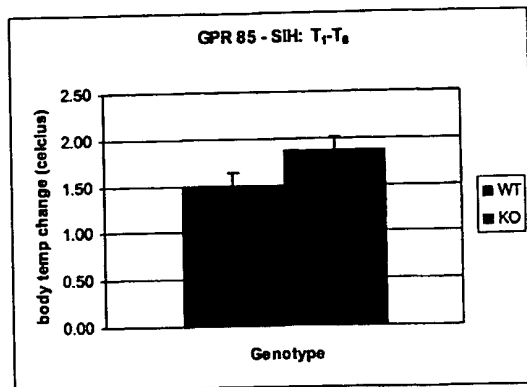


FIGURE 7B.

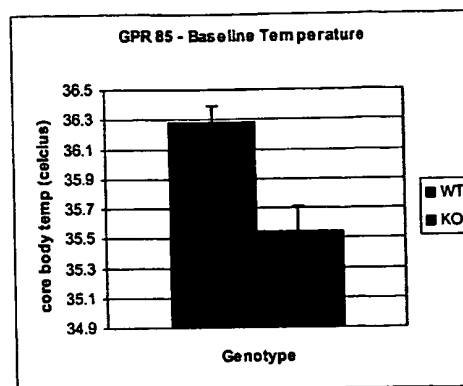


FIGURE 8.

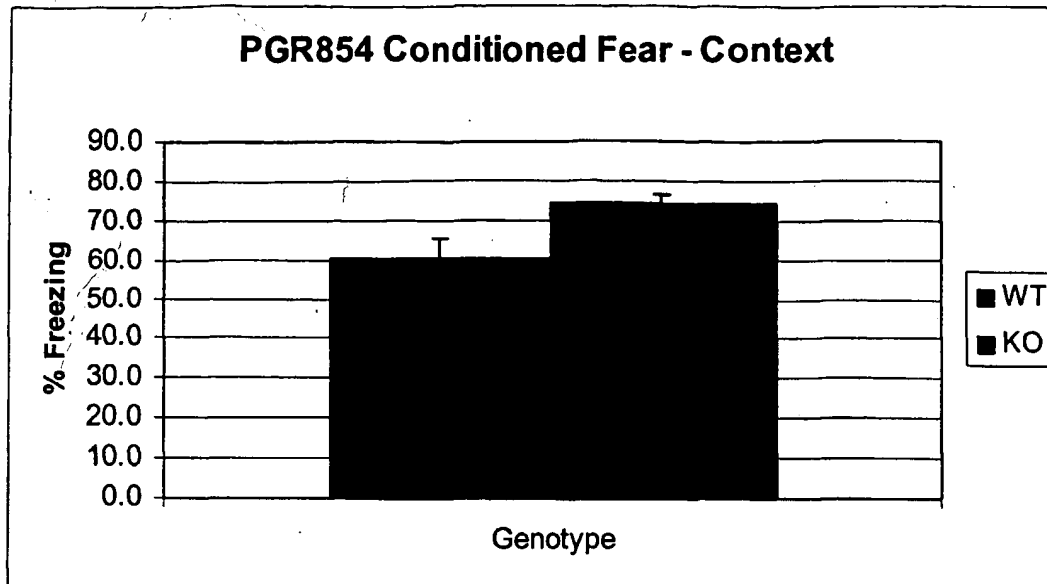


FIGURE 9A.

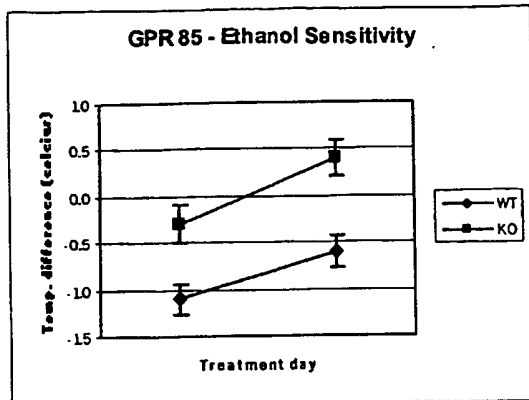
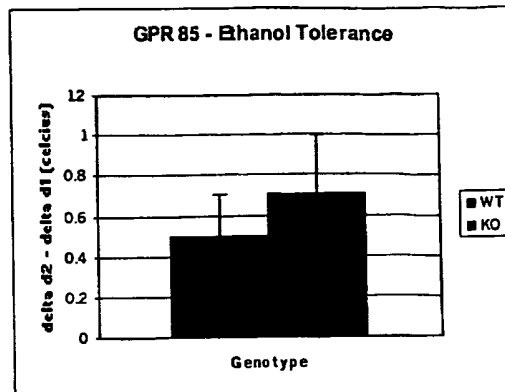


FIGURE 9B.



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